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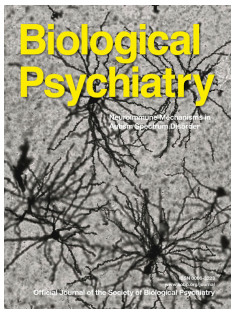

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Genome-wide burden of rare short deletions is enriched in Major Depressive Disorder in four cohorts

Short title: Rare deletions in major depression

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ABSTRACT

Background: Major Depressive Disorder (MDD) is moderately heritable, with high prevalence and presumed high heterogeneity. Copy number variants (CNVs) could contribute to the heritable component of risk, but the two previous genome-wide studies of rare CNVs did not report significant findings.

Methods: In this meta-analysis of four cohorts (5,780 case and 6,626 control subjects), we analyzed association of MDD to (i) genome-wide burden of rare deletions and duplications, partitioned by length (<100 kb or >100kb) and other characteristics; and (ii) individual rare exonic CNVs and CNV regions.

Results: Cases carried significantly more short deletions (P=0.0059), but not long deletions or short or long duplications. The confidence interval for long deletions overlapped with that for short deletions, but the former were 70% less frequent genome-wide, reducing power to detect increased burden. The increased burden of short deletions was primarily in intergenic regions. Short deletions in cases were also modestly enriched for high-confidence enhancer regions. No individual CNV achieved thresholds for suggestive or significant association after genome-wide correction. P-values <0.01 were observed for 15q11.2 duplications (*TUBGCP5*, *CYFIP1*, *NIPA1*, *NIPA2*), deletions in or near *PRKN* or *MSR1*, and exonic duplications of *ATG5*.

Conclusions: The increased burden of short deletions in cases suggests that rare CNVs increase MDD risk by disrupting regulatory regions. Results for longer deletions were less clear, but no large effects were observed for long multigenic CNVs (as seen in schizophrenia and autism). Further studies with larger sample sizes are warranted.

Keywords: major depressive disorder, copy number variation, genome-wide association study, meta-analysis, genetics, neuroscience

Introduction

Major depressive disorder (MDD) is a common psychiatric disorder with a lifetime prevalence of 10-20% (1). It was the third leading cause of global disability in 2015 (2). Heritability is approximately 37%, lower than that of several other psychiatric disorders (3). The genome-wide contribution of common single nucleotide polymorphisms (SNPs) to MDD risk is approximately 20% (4). Consistent with the moderate heritability and high population prevalence, it has required greater than 100,000 MDD cases to detect large numbers of genome-wide significant SNP associations, e.g., 15 loci in 121,380 cases plus 338,101 controls (5), and 44 loci in a partially-overlapping sample (135,458 cases plus 344,901 controls) (6).

Rare copy number variants (CNVs) could be contributing to the unexplained portion of genetic risk and provide information about disease mechanisms. Two previous MDD studies of longer CNVs reported no significant genome-wide burden in cases (7, 8). Here, to achieve a larger sample size, we performed a meta-analysis of the association of MDD to rare CNVs in 5,780 case and 6,626 control subjects from four cohorts. A significant increase of rare, shorter deletions (<100,000 bp) was observed in MDD cases, driven by CNVs in intergenic regions.

Methods and Materials

Samples. We studied four European-ancestry cohorts (***Table 1***). All participants gave signed informed consent under protocols approved by the relevant Institutional Review Boards.

(A) The ***RADIANT*** cohort (7) included cases from three studies of recurrent MDD and two control cohorts (458 controls who were screened for lifetime absence of psychiatric disorder; and 2,699 controls from phase 2 of the National Blood Service (NBS) WTCCC subcohort). Cases were interviewed with the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (9) and diagnosed with ICD-10 or DSM-IV criteria. Exclusion criteria were: any history or family history of schizophrenia or bipolar disorder, or history of mood disorder secondary to alcohol/substance misuse or of mood-incongruent psychosis (7).

(B) ***NESDA/NTR***. Cases and controls were drawn from the Netherlands Twin Register (NTR) (10) and the Netherlands Study of Depression and Anxiety (NESDA) (11). Cases had DSM-IV MDD diagnoses by the Composite Interview Diagnostic Instrument (CIDI) (12).

(C) ***GenRED***. Cases and controls were from the Genetics of Recurrent Early-Onset Depression (GenRED) cohort (13, 14). Cases had a consensus DSM-IV MDD diagnosis based on Diagnostic Interview for Genetic Studies (DIGS) interview and other information, with recurrence or chronicity (an episode lasting ≥3 years), onset <age 31, ≥1 sibling or parent with recurrent MDD and onset <41, MDD independent of substance dependence, no bipolar, schizoaffective disorder or schizophrenia diagnosis, and no suspected bipolar-I parent or sibling. The controls (N=1,345) from the Molecular Genetics of Schizophrenia (MGS) cohort (15) denied (by online screen) ever meeting DSM-IV MDD gate criteria (no two-week period of depressed mood or anhedonia most of the day, nearly every day) – whereas the published GenRED GWAS (13) included controls who never met full MDD criteria by online screen (16).

(D) ***GenRED-II***. Cases were from the second GenRED GWAS wave (same criteria as GenRED). Controls were drawn from the Genomic Psychiatry Cohort (17), Depression Genes and Networks (18), and the Mayo Clinic (19). The control cohorts were screened for lifetime depression with a questionnaire, SCID interview or medical records, respectively.

Genotyping. The RADIANT cases and screened controls were genotyped with the HumanHap 610-Quad Beadchip (Illumina, Inc., San Diego, CA, USA), and the unscreened NBS samples with Illumina Infinium 1M beadchips (hg18 for both) (7). The NTR/NESDA (20) and GenRED cohorts were genotyped with the Affymetrix Human Genome-Wide SNP 6.0 Array (Affymetrix, Santa Clara, CA, USA) (hg18) (14); and GenRED II cases and controls with the Illumina Omni1-Quad beadchip (hg19) (21).

Selection of CNV calling algorithms. CNVs had been called with PennCNV (22), QuantiSNP (23) and iPattern (24) in the RADIANT dataset (using 562,329 probes common to the two platforms); with Birdsuite (25) and PennCNV (22) in NTR/NESDA; with Birdsuite (25) in GenRED; and with QuantiSNP (23) and PennCNV (22) in GenRED II. There is no consensus “optimal” calling algorithm for each

platform. Various authors use a single calling method (8, 26), agreement between two methods (20, 27), or more complex approaches (28, 29).

Here we conducted a preliminary analysis of CNV call concordance for duplicate genotypes for 115 Affymetrix 6.0 samples and 20 Illumina Human610-Quad samples. For Affymetrix we compared CNVision (28), QuantiSNP (23), PennCNV (22) and Birdsuite (25) and each pair of algorithms, plus the addition of CNVision's pCNV parameter (estimating the probability of a true CNV, based on per-SNP variability of Log R Ratio [LRR] and the number of SNPs consistent with a CNV based on B Allele Frequency [BAF]). For Illumina we compared all algorithms (except Birdsuite) and pairs, and addition of pCNV. We also did the analyses for short (<100 kb) and long (>100 kb) CNVs separately.

For Affymetrix, Birdsuite had the highest concordance rate (deletions and duplications), whereas combining it with any other method slightly increased concordance but excluded >40% of calls (***Table S1***). Therefore we used Birdsuite alone for Affymetrix data. For Illumina data, QuantiSNP alone had the best concordance for deletions (***Table S2***). For duplications, concordance was highest for QuantiSNP alone; calls made by both PennCNV and QuantiSNP showed improved concordance but excluded >30% of calls. We used QuantiSNP for primary analyses, plus a secondary "narrow" QuantiSNP+PennCNV analysis. For both platforms, concordance was similar for shorter and longer CNVs (***Tables S3-S6***).

Quality control of samples and CNV calls. Exclusion criteria for samples were applied to each cohort separately. For NTR/NESDA (20) and GenRED (14), exclusions were applied to samples retained by the original studies, using the previous Birdsuite calls: (1) probe intensity variances >4 standard deviations (SDs) above cohort mean; (2) total number or length of deletions or duplications >3 SDs above the mean; (3) any chromosome with number or length of deletions or duplications >7 SDs above the mean; (4) only autosomal CNVs were called. For Illumina data (RADIANT and GenRED II), we re-called CNVs with QuantiSNP and PennCNV from raw LRR and BAF data. Exclusion criteria for unfiltered calls were: (1) genotype call rate <99%; (2) >5% of SNPs with LRR < -0.5 or > 0.5; (3) >1% of SNPs with LRR < -1; (4) BAF drift > 0.01; (5) LRR SD >0.28, (6) waviness factor <0.05 or >-0.05; (7) total CNV number or length >3 SDs above cohort mean (deletions or duplications).

For both platforms, we removed CNVs with <10 probes, and of Birdsuite calls with LOD score <10 (duplications) or <6 (deletions) and QuantiSNP calls with Maximum Log BF <10. We then merged adjacent deletions (copy numbers 0 or 1) or adjacent duplications (Cn 3 or 4) if the number of probes separating them was <30% of probes in the merged region (iterating through each chromosome until all eligible segments were merged, using an in-house script). We removed CNVs with ≥50% overlap with centromeres, telomeres, segmental duplications, or immunoglobulin genes, or length <10 kb (too few probes to call reliably) or >4 Mb (in previous work (30), CNVs>4 Mb were disproportionately detected in DNA from lymphoblastic cell lines), or with frequency >1% in any of four large-sample cohorts included in the Database of Genomic Variants (DGV) (31-34), or with frequency >1% (based on 50% overlap) in any of our control cohorts.

Statistical analysis overview. All analyses were conducted for post-QC deletions and duplications using PLINK and R. Genomic locations with hg18 coordinates were converted to hg19 (UCSC liftOver tool). We first determined (as described below) that effects of cohort and sex had to be controlled appropriately. We chose primary analyses which directly compute an odds ratio and were equivalent to meta-analysis: logistic regression with sex and cohort covariates (for burden tests) or Cochrane-Mantel-Haenszel (CMH) tests stratified for sex and cohort (for single CNVs), plus meta-analysis and/or permutation tests to check results. We tested two main hypotheses, correcting for multiple tests within each hypothesis:

(1) *Global burden* of rare CNVs is greater in cases vs. controls. The four primary analyses were for deletions and duplications, each subdivided by size (<100kb, >100kb); thus the threshold of significance was P<0.0125 (0.05/4).

(2) Cases are more likely to carry *specific CNVs*. Primary analyses tested association by (i) *gene* (CNVs impacting exon(s) of the gene); and (ii) *CNV region* defined by pools of overlapping CNVs (PLINK). We established thresholds for significant suggestive association as described below (30). Genic tests considered only exonic CNVs because of the stronger mechanistic hypothesis and because exonic

and "genic" CNVs were largely overlapping [***Table S7***] -- 93.2% (deletions) and 99.4% (duplications) of long genic CNVs, and 62.6% and 83.6% of short genic CNVs were exonic.

Effects of cohort and sex. We evaluated two potential confounding variables: cohort; and sex (the female proportion was higher in cases and variable across cohorts). Multiple linear regressions were performed for total rare deletions or duplications per subject or summed length (***Table S8***), with case/control status, cohort and sex as independent variables. There were significant effects for cohort (deletions and duplications) and sex (deletions).

Genome-wide burden analyses were performed for short and long deletions and duplications, using logistic regression with sex and cohort as covariates to test for case-control difference. Secondary analyses considered intergenic and genic CNVs; separate analyses of exonic and intronic-only CNVs; singletons; CNVs >500 kb and >1000 kb; short deletions by 10 kb length bins (10-20, 20-30, etc.). Results were checked against: logistic regression for each cohort (with sex as a covariate) followed by meta-analysis of the beta coefficients and standard errors (R function "metagen" (35)); and permutation tests stratified for cohort and sex (randomly swapping case-control status within the same sex and cohort 100,000 times using PLINK's "--within" option).

Down-sampled analysis. As a check on the effects of uneven numbers of cases/controls and males/females per cohort, we repeated burden analyses using a down-sampled dataset: 1,622 male and female cases and controls (6,488 total) drawn from each cohort proportional to its size (***Table S9***).

Analyses of single CNVs. We performed one-sided CMH tests (stratified by sex and cohort) of a case excess of exonic CNVs impacting each RefSeq gene, and of CNVs in each "CNV region"; and checked results with a stratified permutation tests (results were almost identical). To define regions, we used PLINK's "--segment-group" command to identify 994 CNV "pools" of overlapping post-QC CNVs (from all cohorts), and termed the union a *CNV region.*

For any CNV with nominally increased case frequency (CMH P<0.01), we carried out additional filtering because calling artifacts often produce "significant" results for rare events. We visualized regional LRR and BAF plots for all carriers and a threefold number of non-carriers, and superimposed on

LRR a plot of estimated probe-by-probe copy number using a different algorithm (36). We also plotted all CNVs in the region. We excluded CNVs for which the probewise algorithm showed no copy number change. After excluding genes/regions where most calls were considered artifacts, or were the edges of a common CNV region, we re-computed the CMH tests. We computed a proportion test across the four cohorts for each gene/region and excluded those with significant heterogeneity (P<3.53E-05 to correct for multiple tests, see below). ***Table S10*** lists the inspected regions and reasons for all exclusions.

Additional exploratory analyses (permutation tests) considered each transcript (http://genome.ucsc.edu/), ENCODE regulatory region, Roadmap Project putative enhancer, promoter and dyadic region, and in aggregate for lists of CNVs with reported associations to psychiatric disorders (29, 37) or developmental delay (32).

We used a previously-described method (30) to estimate thresholds for significant association (expected by chance once in 20 genome-wide studies) and suggestive association (expected once per study). For all 994 CNV regions, the 329 deletion regions intersected with 487 genes, and 665 duplication regions intersected with 1,475 genes (totaling 1,962 genic tests). However, tests of genes within a region are correlated, and each region contained 4.64 genes on average. Thus the 1,962 genic tests represented ~1962/4.64=423 independent tests. We corrected for 1,417 tests (994 regions and 423 genes), a conservative estimate because some regions were partially overlapping, and many genes were in more than one region, resulting in a P-value threshold for significant association of 0.05/1417=3.53E-05, and for suggestive association, 1.0/1417=7.06E-04.

Power analysis. Power analyses were conducted for detection of specific CNVs (***Figure S1***). For the ranges of allele frequencies and genotypic relative risks that were observed in this study, power was good-excellent to detect associations at P=0.01, but detection of suggestive or significant association would have required larger relative risks than were observed here.

Enrichment analysis of functional pathways. To detect gene sets associated with MDD, pathways from Kyoto Encyclopedia of Genes and Genomes (KEGG, http://rest.kegg.jp/list/pathway) and Gene Ontology (GO, http://geneontology.org/page/download-annotations) were downloaded. Geneset-

enrichment methods (38) were used to test for enrichment of CNVs (separately for all or exonic CNVs) in all the genes of each pathway relative to all genic CNVs using '--cnv-enrichment-test' in PLINK. Permutation tests of enrichment in cases were also performed by adding '--mperm 10000' in PLINK, with batch and sex as covariates. A set of schizophrenia-associated genes (39) was also tested.

We also evaluated whether case CNVs were enriched in high-confidence DNaseI regions (-log10(p)>= 10) from ENCODE (40) or Roadmap Epigenomics Project (41) (downloaded from https://personal.broadinstitute.org/meuleman/reg2map/HoneyBadger2_release/). Separately for promoter, enhancer and dyadic regions, we analyzed all tissues together (i.e., whether more case short deletions intersected with at least one high-confidence regulatory sequence from any tissue), and then each tissue separately (counting high-confidence sequences for that tissue). For intergenic short deletions, averaged across tissues, the proportion of CNVs that overlap high-confidence regulatory regions was 1.3% for promoter regions, 2.0% (dyadic regions) and 14.9% (enhancer regions).

RESULTS

Of 14,429 samples, 12,406 passed QC (5,780 cases and 6,626 controls, ***Table 1***). Total numbers of rare deletion and duplication calls are shown in ***Table S11***.

Genome-wide burden. Cases had more CNVs per subject for rare, short (<100 kb) deletions (P=0.00592, odds ratio = 1.0483), driven by intergenic deletions (P=0.00714, OR=1.0716) (***Table 2***; and by cohort, ***Table S12***). Similar results were observed by the primary logistic regression tests (***Table S13***), meta-analysis of cohort-specific logistic regressions (***Table S14***), stratified permutation tests (***Table S7***) and the downsampled dataset (***Table S9***). Short deletions across the 10-100kb range contributed to the case-control difference (***Table S15; Figures S2-S3***). No significant differences were observed for duplications or long deletions, but the OR for long deletions was positive (1.03), the confidence interval overlapped with that for short deletions (***Table 2***), and a secondary analysis of all rare deletions was significant (OR=1.044; CI=1.013-1.075; P=0.0046; ***Table S16***). No significant effect was observed for singleton or very long (>500 kb, > 1000 kb) deletions or duplications. There was no evidence of strong heterogeneity by cohort for short deletions (Cochran's Q-test; P=0.31) or short intergenic deletions

(P=0.14) (***Table S14***; and ***Table S12*** and ***Figure S4*** for results by cohort). The excess of short deletions in cases became more significant when CNVs with frequency >1% in each cohort separately were excluded (rather than >1% in any cohort) (***Table S17***); or when QuantiSNP+PennCNV calls were required for Illumina data (***Table S18***). Burden results did not change after excluding nominally significant CNV regions that failed manual checks (***Table S19***).

We considered two possible within-cohort confounding factors: DNA source and genotyping platforms. In GenRED II, there were two DNA sources: blood (137 cases and all controls) or lymphoblastic cell lines (674 cases) **(*Table S20***). CNV burden did not significantly differ between blood vs. LCL case DNAs for any category, with a trend for more *long* deletions in LCL DNA (***Table S21***). RADIANT CNV calls used probes common to Illumina 610-Quad (assayed in cases and screened controls) and Illumina 1M (unscreened controls). Burden results were similar for cases vs. screened or unscreened controls, except that cases had more short deletions than *screened* controls (assayed with the same array) (***Table S22***). Thus, neither factor accounted for the main finding.

Exonic CNVs and CNV regions. After all QC, no gene or region met criteria for significant or suggestive association (***Table S10***). Results with P<0.01 are shown in ***Table 3.*** These represent four independent loci. Duplications in 15q11.2 achieved P=0.00076 (OR=3.88). These duplications are reciprocal to a well-known deletion region (see Discussion), consistently impacting four genes. Less consistent results are observed in surrounding genes in segmental duplication regions (***Table S10***). Exonic deletions in *MSR1* achieve P=0.0019 (OR=1.96); the region test includes several intronic deletions, with a similar result (P=0.00075, OR=2.05). A CNV region containing exonic and intronic deletions in *PRKN* (formerly *PARK2*) produced P=0.00097 (OR=1.92); the exonic test for *PRKN* had P>0.01. Finally, there were 6 duplications, all in cases, in 6q21 (P=0.0059, OR=∞), including 5 exonic duplications in *ATG5* that overlapped with one upstream duplication. LRR/BAF plots of CNVs shown in ***Table 3*** are provided in ***Figure S5***.

Pathway enrichment analysis. After correction for multiple testing, no KEGG or GO pathway was enriched with short deletions in cases.

Regulatory regions. Enhancer regions were modestly enriched in cases for all tissues combined as defined above (P=0.024), and in 5 of 127 specific tissues (P<0.05) (***Table S23***).

Known loci associated with psychiatric disorders or developmental delay. Permutation tests did not demonstrate case enrichment of CNVs in loci associated with psychiatric disorders (***Table S24***) or developmental delay (***Table S25***). There was no overlap between the CNVs reported in ***Table 3*** and significant MDD GWAS loci (6, 42).

Discussion

This is the largest genome-wide study to date of the association of MDD with rare CNVs. An excess of long CNVs (>100 kb) was initially reported in an analysis of the RADIANT cohort that included additional controls with DNA from buccal swabs (43), but a subsequent re-analysis (without the extra controls and with stricter QC, producing a substantial reduction in number of CNVs per subject similar to that reported here) detected no significant excess (7). Another study of longer CNVs in 452 treatment-resistant depression cases and 811 controls also reported no significant differences (8). For schizophrenia, evidence for association of several long CNVs with large effects on risk could be detected with samples comparable in size to RADIANT (44). There were no such findings for single CNVs in the present, larger study. Thus it appears that very long, multigenic CNVs are less likely to have large effects on the risk of MDD.

Global burden of short deletions. We observed enrichment of short deletions (<100 kb) in cases, and particularly intergenic deletions. This suggests that the effect on MDD risk is due to deletion of regulatory elements, consistent with the (modest) enrichment of high-confidence enhancer regions in short deletions in cases. This is consistent with the extensive analyses of the Psychiatric Genomics Consortium's meta-analysis of depression GWAS data (6) which detected 44 significant associations primarily in non-exonic SNPs, including several in genes that are involved with extensive regulatory networks (*RBFOX1, RBFOX2, RBFOX3, CELF4*), as well as genome-wide enrichment of highly conserved regions, open chromatin in human brain and an epigenetic mark of active enhancers (H3K4me1).

One might expect an increased burden of longer CNVs as well, because they contain more genes and regulatory elements. We analyzed short and long deletions separately because longer CNVs have been more frequently implicated in disease risk. Similar ORs were observed for burden of short and of long deletions in cases, and their confidence intervals overlapped, but we had less power to detect an excess of long deletions because they were 70% less frequent than short deletions. Thus, an increased burden of longer deletions might be observed in larger meta-analyses. We also suspect that the ascertainment methods of most MDD studies are biased against individuals with long multigenic CNVs, whose carriers are at higher risk of disorders such as schizophrenia, autism and intellectual disability. Individuals with these phenotypes are at increased risk of depression (45, 46), but they are often excluded from MDD cohorts, and are often not specifically diagnosed with, or treated for, depression (resulting in exclusion even from registry-based cohorts). Thus, both short and long rare deletions could impact on risk of MDD, but the current results are significant only for shorter deletions (10-100kb), and larger cohorts will be needed to resolve the issue.

Individual genes and regions. No significant or suggestive associations were detected for individual exonic CNVs or for CNV regions, after conservative correction for genome-wide testing. Larger datasets will be needed to identify true positive findings. Nominal association was observed in several regions ($P<0.01$ but not achieving suggestive or significant thresholds): (i) 15q11.2 duplications encompassing the small, non-imprinted BP1-BP2 segment of the Prader-Willi/Angelman region. Deletions of this segment are weakly associated with risk of schizophrenia (29, 37), and have been reported to be associated with dyslexia and dyscalculia (with deletions and duplications associated with reductions or increases, respectively, in size and activity of the left fusiform gyrus) (47). (ii) Deletions in exons of *MSR1* (Macrophage Scavenger Receptor 1) (or all deletions in that region), implicated in atherosclerosis, Alzheimer's disease and host defense. (iii) Deletions in 6q26 impacting introns or exons of *PRKN* (Parkin RBR E3 Ubiquitin Protein Ligase), where recessive mutations cause early-onset Parkinson's disease (PD) (type 2) but heterozygous variants are not associated with PD (48), although PD is associated with increased depressive symptoms (49). (iii) Duplications in exons of, or upstream sequence near, *ATG5*

(Autophagy Related 5). *ATG5* has multiple immune functions including negative regulation of the type I interferon production pathway, which is of note because reduced white blood cell expression of interferon I response genes was reported (18), but not replicated (50) in studies of MDD.

Limitations. The sample size is larger than previous CNV studies of MDD, but remains underpowered. Combining CNV cohorts presents challenges including differences in clinical methods (inclusion criteria, ascertainment, assessments) and genotyping (platforms which differ in genome coverage and signal:noise ratio). Also, the present cohorts are not ideal for testing whether the long, multigenic "neuropsychiatric" CNVs are also predisposing for depression: the psychiatric and neurological features of these CNVs may be considered exclusion criteria from MDD studies; and the associated cognitive impairments reduce the probability of being recruited into MDD cohorts because individual carriers are less likely to volunteer or to be treated in the targeted clinical settings. On the other hand, the cohorts are broadly representative of the current concept of clinically significant MDD.

Conclusion. In MDD cases from four cohorts, we found significant evidence for an increased global burden of shorter rare deletions, which was mainly driven by intergenic deletions. The evidence regarding longer deletions was inconclusive: they were not significantly increased in cases, but the confidence intervals overlapped with the case-control ORs for shorter and longer deletions, and there was less power to detect a difference because longer deletions are less frequent. Overall, the results suggest that the effects of CNVs on regulatory elements, primarily in intergenic regions, play a role in predisposition to MDD.

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The authors report no biomedical financial interests or potential conflicts of interest.

Availability of data and biomaterials

Biomaterials and clinical data are available from the NIMH repository (https://nimhgenetics.org) for the GenRED cases (the GenRED1 cohort includes the family-based linkage cohort and part of the subsequent case collection; the GenRED2 cohort includes the remainder of the case collection); for the MGS controls; and for Genomic Psychiatry Cohort controls, including the Mayo Clinic controls.

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Table 1. Cohorts and sample sizes before and after QC filtering

Cohort	Pre-QC Sample Size		Post-QC Sample Size	
	Cases (Male/Female)	Controls (Male/Female)	Cases (Male/Female)	Controls (Male/Female)
RADIANT	3,087 (908/2,179)	3,157 (1,522/1,635)	2,460 (724/1,736)	2,587 (1,240/1,347)
NESDA/NTR	1,637 (509/1,128)	2,030 (765/1,265)	1,568 (488/1,080)	1,913 (719/1,194)
GenRED I	1,089 (319/770)	1,345 (784/561)	941 (271/670)	1,264 (743/521)
GenRED II	831 (144/687)	944 (418/526)	811 (139/672)	862 (384/478)
Total	6,644 (1,880/4,764)	7,476 (3,489/3,987)	5,780 (1,622/4,158)	6,626 (3,086/3,540)

Table 2. Genome-wide burden analyses of long and short deletions and duplications (CNVs/subject)

CNV type	CNVs/subject		OR	95% CI	p value
	Cases	Cont			
Deletions					
>100kb — All	0.324	0.318	1.0296	0.9658-1.0975	3.71E-01
Intergenic	0.134	0.138	0.9881	0.8956-1.0899	8.11E-01
Genic	0.191	0.181	1.0606	0.9754-1.1531	1.68E-01
Exonic	0.175	0.168	1.0521	0.9646-1.1475	2.51E-01
Intronic	0.015	0.012	1.1672	0.8591-1.5876	3.23E-01
<100kb — All	1.015	0.978	1.0483	1.0139-1.0843	***5.92E-03***
Intergenic	0.506	0.483	1.0716	1.0190-1.1270	*7.14E-03*
Genic	0.509	0.495	1.0343	0.9877-1.0842	1.56E-01
Exonic	0.330	0.310	1.0552	0.9965-1.1192	6.95E-02
Intronic	0.179	0.185	0.9952	0.9149-1.0825	9.11E-01
Duplications					
>100kb — All	0.496	0.476	1.0268	0.9837-1.0725	2.29E-01
Intergenic	0.087	0.079	1.0912	0.9654-1.2333	1.62E-01
Genic	0.409	0.397	1.0187	0.9723-1.0677	4.37E-01
Exonic	0.406	0.395	1.0166	0.9702-1.0657	4.89E-01
Intronic	0.004	0.002	1.5254	0.7880-3.0095	2.13E-01
<100kb — All	0.670	0.702	0.9850	0.9512-1.0194	3.90E-01
Intergenic	0.252	0.266	0.9788	0.9166-1.0449	5.21E-01
Genic	0.418	0.436	0.9845	0.9410-1.0296	4.96E-01
Exonic	0.345	0.365	0.9730	0.9253-1.0225	2.83E-01
Intronic	0.073	0.072	1.0586	0.9285-1.2066	3.94E-01

For rare CNVs (carried by <1% of controls in each cohort), we defined four primary case-control tests of CNV subsets: deletions and duplications, and within each type, long (>100kb) and short (<100kb). For each subset, case-control difference in CNVs per subject was tested by logistic regression, stratified for cohort and sex (Bonferroni-corrected threshold of significance p=0.05/4=0.0125 (significant result shown in ***bold italics***). Further exploration then considered genomic location: only intergenic, genic (exonic and/or intronic impact), exonic (subset of genic), and only intronic (subset of genic). See Table S8 for complete results.

Table 3. CNV genes and regions (p<0.01 case-control difference)

Gene or region	Chr	Start	End	ALL		CMH test		RAD		GR2		GR1		Neth		Annotation
				Case	Cont	OR	p	Ca	Co	Ca	Co	Ca	Co	Ca	Co	
Genes (exonic)																
Del																
MSR1	8	15,965,386	16,050,300	55	32	1.96	1.9E-03	23	10	6	3	15	10	11	9	
Dup																
TUBGCP5	15	22,833,394	22,873,891	24	7	3.88	7.6E-04	7	3	11	0	2	1	4	3	15q11.2 (reciprocal to well-known deletion region)
CYFIP1	15	22,892,648	23,003,603													
NIPA2	15	23,004,683	23,034,427													
NIPA1	15	23,043,278	23,086,843													
Regions (genic and/or intergenic)																
Del																
6q26	6	162,136,159	163,489,668	65	40	1.92	9.7E-04	33	17	10	11	9	5	13	7	*PRKN*
8p22	8	15,817,196	16,092,656	59	33	2.05	7.5E-04	24	10	18	11	6	3	11	9	*MSR1*
Dup																
6q21	6	106,549,398	107,026,323	6	0	Inf	5.9E-03	2	0	1	0	0	0	3	0	*ATG5*
15q11.2	15	22,652,330	23,309,294	24	7	3.88	7.6E-04	7	3	2	1	11	0	4	3	*TUBGCP5, CYFIP1, NIPA1, NIPA2*

Shown are the numbers of cases (out of 5,780) and of controls (out of 6,626) carrying each CNV with post-QC P<0.01. Del=deletions; Dup=duplications; Chr=chromosome; Start and End are genomic positions in base pairs (build HG19) either for the gene for which one or more exons was impacted by each CNV, or for the region within which CNVs were counted. Cont=control; CMH=Cochrane-Mantel-Haenszel; OR = CMH odds ratio; Ca=case; Co=controls; GR2=GenRED2 (Illumina); GR1=GenRED1 (Affymetrix); Neth=NESDA/NTR (Affymetrix); RAD = RADIANT cohort (Illumina platform).

Genome-wide Burden of Rare Short Deletions Is Enriched in Major Depressive Disorder in Four Cohorts

Supplementary Information

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Comparative analyses of multiple CNV calling algorithms

Concordance analyses were restricted to calls after quality control. But when considering whether a call in specimen 1 was concordant with specimen 2, we used CNV calls of Specimen 2 before quality control as even a sub-threshold call could provide some evidence for the existence of a CNV. A CNV call was considered to be concordant if 50% length of the call in specimen 1 is overlapped by the call in specimen 2.

Table S1. Concordance rate of CNV calls between duplicate samples genotyped with Affymetrix array.

CNVision cutoff	115 duplicate pairs	Affymetrix Deletions									
		CNVision	PennCNV	PennCNV + QuantiSNP	PennCNV + Birdsuite	QuantiSNP	QuantiSNP + PennCNV	QuantiSNP + Birdsuite	Birdsuite	Birdsuite + QuantiSNP	Birdsuite + PennCNV
No filtering	# S1	12.56	11.36	10.78	10.41	11.12	10.40	10.18	20.10	11.12	10.41
	# S2	12.44	11.44	10.89	10.56	11.00	10.35	10.17	20.46	11.17	10.42
	% S1 by S2	0.77	0.79	0.82	0.82	0.84	0.86	0.86	0.92	0.95	0.95
	% S2 by S1	0.80	0.82	0.84	0.85	0.86	0.88	0.88	0.91	0.95	0.97
pCNV<0.05	# S1	10.47	9.73	9.45	9.06	9.83	9.43	9.16	9.28	8.90	8.68
	# S2	10.18	9.55	9.30	8.98	9.65	9.32	9.07	8.93	8.69	8.50
	% S1 by S2	0.83	0.84	0.85	0.86	0.86	0.87	0.88	0.95	0.96	0.96
	% S2 by S1	0.85	0.87	0.88	0.88	0.89	0.90	0.90	0.97	0.97	0.98
pCNVIrr<0.05	# S1	11.68	10.72	10.26	9.88	10.48	9.98	9.68	10.54	9.85	9.50
	# S2	11.57	10.85	10.47	10.11	10.47	10.03	9.77	10.75	9.90	9.57
	% S1 by S2	0.79	0.80	0.82	0.83	0.84	0.86	0.86	0.94	0.96	0.96
	% S2 by S1	0.82	0.84	0.85	0.86	0.87	0.88	0.88	0.96	0.97	0.97
pCNVbaf<0.05	# S1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.02	0.01	0.01
	# S2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	% S1 by S2	NA	NA	NA	NA	NA	NA	NA	0.50	1.00	1.00
	% S2 by S1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
pCNV<0.05 or pCNVIrr<0.05	# S1	11.68	10.72	10.26	9.88	10.48	9.98	9.68	10.54	9.85	9.50
	# S2	11.57	10.85	10.47	10.11	10.47	10.03	9.77	10.75	9.90	9.57
	% S1 by S2	0.79	0.80	0.82	0.83	0.84	0.86	0.86	0.94	0.96	0.96
	% S2 by S1	0.82	0.84	0.85	0.86	0.87	0.88	0.88	0.96	0.97	0.97
pCNV<0.05 or pCNVbaf<0.05	# S1	10.47	9.73	9.45	9.06	9.83	9.43	9.16	9.29	8.91	8.69
	# S2	10.18	9.55	9.30	8.98	9.65	9.32	9.07	8.93	8.69	8.50
	% S1 by S2	0.83	0.84	0.85	0.86	0.86	0.87	0.88	0.95	0.96	0.96
	% S2 by S1	0.85	0.87	0.88	0.88	0.89	0.90	0.90	0.97	0.97	0.98
pCNVIrr<0.05 or pCNVbaf<0.05	# S1	11.68	10.72	10.26	9.88	10.48	9.98	9.68	10.55	9.86	9.50
	# S2	11.57	10.85	10.47	10.11	10.47	10.03	9.77	10.75	9.90	9.57
	% S1 by S2	0.79	0.80	0.82	0.83	0.84	0.86	0.86	0.94	0.96	0.96
	% S2 by S1	0.82	0.84	0.85	0.86	0.87	0.88	0.88	0.96	0.97	0.97
pCNV<0.05 or pCNVIrr<0.05 or pCNVbaf<0.05	# S1	11.68	10.72	10.26	9.88	10.48	9.98	9.68	10.55	9.86	9.50
	# S2	11.57	10.85	10.47	10.11	10.47	10.03	9.77	10.75	9.90	9.57
	% S1 by S2	0.79	0.80	0.82	0.83	0.84	0.86	0.86	0.94	0.96	0.96
	% S2 by S1	0.82	0.84	0.85	0.86	0.87	0.88	0.88	0.96	0.97	0.97

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CNVision cutoff	115 duplicate pairs	Affymetrix Duplications									
		CNVision	PennCNV	PennCNV + QuantiSNP	PennCNV + Birdsuite	QuantiSNP	QuantiSNP + PennCNV	QuantiSNP + Birdsuite	Birdsuite	Birdsuite + QuantiSNP	Birdsuite + PennCNV
No filtering	# S1	9.34	8.27	7.42	4.15	8.39	7.27	4.04	5.68	3.00	2.97
	# S2	9.72	8.57	7.88	4.36	8.76	7.51	4.45	5.80	3.13	3.02
	% S1 by S2	0.70	0.72	0.74	0.80	0.76	0.79	0.83	0.81	0.92	0.92
	% S2 by S1	0.68	0.70	0.73	0.74	0.73	0.76	0.79	0.79	0.94	0.94
pCNV<0.05	# S1	1.76	1.64	1.59	1.47	1.71	1.66	1.50	1.43	1.37	1.36
	# S2	1.58	1.63	1.58	1.42	1.63	1.58	1.43	1.27	1.25	1.25
	% S1 by S2	0.85	0.88	0.88	0.90	0.87	0.89	0.89	0.95	0.97	0.97
	% S2 by S1	0.90	0.89	0.90	0.91	0.95	0.95	0.97	0.97	0.97	0.97
pCNVlrr<0.05	# S1	6.61	6.18	5.76	3.01	6.38	5.80	2.97	2.46	2.28	2.28
	# S2	6.47	6.07	5.87	2.97	6.50	5.88	3.18	2.36	2.26	2.18
	% S1 by S2	0.73	0.75	0.76	0.82	0.78	0.80	0.82	0.93	0.95	0.95
	% S2 by S1	0.72	0.75	0.76	0.78	0.77	0.80	0.82	0.94	0.95	0.95
pCNVbaf<0.05	# S1	0.99	0.97	0.94	0.90	0.97	0.94	0.90	0.90	0.85	0.85
	# S2	0.90	0.94	0.90	0.88	0.89	0.87	0.85	0.85	0.83	0.83
	% S1 by S2	0.91	0.91	0.91	0.93	0.91	0.92	0.91	0.96	0.97	0.97
	% S2 by S1	0.94	0.90	0.91	0.90	0.97	0.97	0.97	0.99	0.99	0.99
pCNV<0.05 or pCNVlrr<0.05	# S1	6.85	6.38	5.92	3.18	6.58	5.97	3.16	2.67	2.47	2.45
	# S2	6.67	6.30	6.10	3.19	6.71	6.09	3.39	2.56	2.46	2.37
	% S1 by S2	0.74	0.76	0.77	0.83	0.79	0.81	0.83	0.94	0.95	0.95
	% S2 by S1	0.74	0.75	0.76	0.79	0.78	0.81	0.83	0.95	0.95	0.96
pCNV<0.05 or pCNVbaf<0.05	# S1	1.81	1.69	1.63	1.50	1.75	1.70	1.53	1.44	1.38	1.37
	# S2	1.62	1.66	1.60	1.43	1.64	1.58	1.44	1.29	1.26	1.27
	% S1 by S2	0.84	0.88	0.89	0.90	0.87	0.89	0.89	0.95	0.97	0.97
	% S2 by S1	0.90	0.90	0.90	0.91	0.95	0.95	0.97	0.97	0.97	0.97
pCNVlrr<0.05 or pCNVbaf<0.05	# S1	6.87	6.41	5.96	3.21	6.60	5.99	3.17	2.67	2.46	2.45
	# S2	6.71	6.32	6.10	3.19	6.71	6.08	3.39	2.57	2.46	2.38
	% S1 by S2	0.74	0.76	0.77	0.83	0.79	0.81	0.84	0.94	0.95	0.95
	% S2 by S1	0.74	0.75	0.77	0.79	0.78	0.80	0.83	0.95	0.95	0.96
pCNV<0.05 or pCNVlrr<0.05 or pCNVbaf<0.05	# S1	6.89	6.43	5.96	3.22	6.62	6.01	3.18	2.69	2.48	2.47
	# S2	6.71	6.34	6.11	3.21	6.72	6.09	3.40	2.57	2.47	2.39
	% S1 by S2	0.74	0.76	0.77	0.83	0.79	0.81	0.84	0.94	0.95	0.95
	% S2 by S1	0.74	0.75	0.77	0.79	0.78	0.81	0.83	0.95	0.95	0.96

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CNVision cutoff	115 duplicate pairs	Affymetrix All CNVs									
		CNVision	PennCNV	PennCNV + QuantiSNP	PennCNV + Birdsuite	QuantiSNP	QuantiSNP + PennCNV	QuantiSNP + Birdsuite	Birdsuite	Birdsuite + QuantiSNP	Birdsuite + PennCNV
No filtering	# S1	21.90	19.63	18.20	14.56	19.51	17.67	14.23	25.78	14.12	13.38
	# S2	22.16	20.01	18.77	14.91	19.76	17.86	14.62	26.26	14.30	13.43
	% S1 by S2	0.74	0.76	0.78	0.81	0.81	0.83	0.85	0.90	0.95	0.95
	% S2 by S1	0.74	0.76	0.78	0.81	0.80	0.82	0.85	0.89	0.95	0.96
pCNV<0.05	# S1	12.24	11.37	11.04	10.53	11.55	11.10	10.66	10.70	10.28	10.03
	# S2	11.76	11.17	10.88	10.40	11.29	10.90	10.50	10.20	9.94	9.75
	% S1 by S2	0.83	0.85	0.86	0.86	0.86	0.88	0.88	0.95	0.96	0.96
	% S2 by S1	0.85	0.87	0.88	0.89	0.89	0.91	0.91	0.97	0.97	0.97
pCNVIrr<0.05	# S1	18.29	16.90	16.02	12.89	16.86	15.78	12.65	13.00	12.13	11.77
	# S2	18.04	16.92	16.34	13.09	16.97	15.91	12.95	13.10	12.16	11.75
	% S1 by S2	0.77	0.78	0.80	0.83	0.82	0.83	0.85	0.94	0.96	0.96
	% S2 by S1	0.78	0.80	0.81	0.84	0.82	0.84	0.86	0.95	0.96	0.96
pCNVbaf<0.05	# S1	0.99	0.97	0.94	0.90	0.97	0.94	0.90	0.91	0.86	0.86
	# S2	0.90	0.94	0.90	0.88	0.89	0.87	0.85	0.85	0.83	0.83
	% S1 by S2	0.91	0.91	0.91	0.93	0.91	0.92	0.91	0.95	0.97	0.97
	% S2 by S1	0.94	0.90	0.91	0.90	0.97	0.97	0.97	0.99	0.99	0.99
pCNV<0.05 or pCNVIrr<0.05	# S1	18.53	17.10	16.18	13.06	17.06	15.96	12.83	13.21	12.32	11.95
	# S2	18.24	17.16	16.57	13.30	17.18	16.12	13.16	13.30	12.36	11.94
	% S1 by S2	0.77	0.78	0.80	0.83	0.82	0.84	0.85	0.94	0.96	0.96
	% S2 by S1	0.78	0.80	0.81	0.84	0.82	0.84	0.86	0.95	0.96	0.96
pCNV<0.05 or pCNVbaf<0.05	# S1	12.28	11.42	11.08	10.57	11.58	11.13	10.69	10.73	10.30	10.06
	# S2	11.80	11.21	10.90	10.42	11.30	10.90	10.51	10.22	9.95	9.77
	% S1 by S2	0.83	0.85	0.86	0.87	0.86	0.88	0.88	0.95	0.96	0.96
	% S2 by S1	0.86	0.87	0.88	0.89	0.89	0.91	0.91	0.97	0.97	0.97
pCNVIrr<0.05 or pCNVbaf<0.05	# S1	18.55	17.13	16.22	13.09	17.08	15.97	12.84	13.22	12.32	11.96
	# S2	18.28	17.17	16.57	13.30	17.18	16.11	13.16	13.31	12.36	11.95
	% S1 by S2	0.77	0.78	0.80	0.83	0.82	0.84	0.85	0.94	0.96	0.96
	% S2 by S1	0.78	0.80	0.81	0.84	0.82	0.84	0.86	0.95	0.96	0.96
pCNV<0.05 or pCNVIrr<0.05 or pCNVbaf<0.05	# S1	18.57	17.15	16.22	13.10	17.10	15.99	12.86	13.23	12.34	11.97
	# S2	18.29	17.19	16.58	13.32	17.19	16.12	13.17	13.32	12.37	11.96
	% S1 by S2	0.77	0.78	0.80	0.83	0.82	0.84	0.85	0.94	0.96	0.96
	% S2 by S1	0.78	0.80	0.81	0.84	0.82	0.84	0.86	0.95	0.96	0.96

S1,2 = N(CNVs) detected in sample 1 or 2 of each pair of duplicates.
% S1 by S2 = proportion of S1 CNVs detected (50% overlap) in S2 - with no filtering of S2.
Method1+Method2 = results when CNVs detected by Method1 were restricted to those also detected by Method2.

Table S2. Concordance rate of CNV calls between duplicate samples genotyped with Illumina array.

CNVision cutoff	20 duplicate pairs	Illumina All CNVs					Illumina Deletions					Illumina Duplications				
		CNVision	PennCNV	QuantiSNP	QuantiSNP + PennCNV	PennCNV + QuantiSNP	CNVision	PennCNV	QuantiSNP	QuantiSNP + PennCNV	PennCNV + QuantiSNP	CNVision	PennCNV	QuantiSNP	QuantiSNP + PennCNV	PennCNV + QuantiSNP
No filtering	# S1	8.95	7.70	8.10	6.15	6.70	6.40	5.00	4.60	3.80	4.60	2.55	2.70	3.50	2.35	2.10
	# S2	8.70	7.60	7.80	6.00	6.75	6.35	5.25	4.55	3.95	4.75	2.35	2.35	3.25	2.05	2.00
	% S1 by S2	0.86	0.87	0.89	0.97	0.93	0.94	0.96	1.00	1.00	0.98	0.59	0.65	0.74	0.88	0.73
	% S2 by S1	0.86	0.87	0.91	0.96	0.92	0.93	0.86	0.94	0.95	0.89	0.69	0.81	0.89	0.99	0.92
pCNV < 0.05	# S1	6.15	5.50	5.60	4.95	5.35	4.50	3.85	3.65	3.15	3.75	1.65	1.65	1.95	1.80	1.60
	# S2	6.05	5.40	5.50	4.95	5.35	4.35	3.60	3.45	3.10	3.55	1.70	1.80	2.05	1.85	1.80
	% S1 by S2	0.94	0.94	0.98	0.98	0.95	0.98	0.96	1.00	1.00	0.97	0.82	0.87	0.92	0.93	0.87
	% S2 by S1	0.96	0.94	0.98	0.99	0.94	1.00	0.92	0.98	0.99	0.91	0.85	0.99	0.99	0.99	0.99
pCNVIrr < 0.05	# S1	7.15	6.20	6.35	5.10	5.65	5.05	4.20	4.05	3.40	4.10	2.10	2.00	2.30	1.70	1.55
	# S2	6.80	5.85	6.30	4.90	5.55	4.90	4.15	3.95	3.40	4.05	1.90	1.70	2.35	1.50	1.50
	% S1 by S2	0.88	0.88	0.92	0.96	0.92	0.98	0.97	1.00	1.00	0.97	0.62	0.66	0.79	0.84	0.75
	% S2 by S1	0.90	0.88	0.95	0.99	0.91	0.96	0.87	0.98	0.99	0.88	0.73	0.87	0.91	0.99	0.99
pCNVbaf < 0.05	# S1	1.30	1.35	1.65	1.50	1.35	0.00	0.00	0.00	0.00	0.00	1.30	1.35	1.65	1.50	1.35
	# S2	1.50	1.60	1.80	1.60	1.60	0.00	0.00	0.00	0.00	0.00	1.50	1.60	1.80	1.60	1.60
	% S1 by S2	0.93	0.96	0.98	1.00	0.96	NA	NA	NA	NA	NA	0.93	0.96	0.98	1.00	0.96
	% S2 by S1	0.87	1.00	1.00	1.00	1.00	NA	NA	NA	NA	NA	0.87	1.00	1.00	1.00	1.00
pCNV < 0.05 or pCNVIrr < 0.05	# S1	7.35	6.50	6.80	5.45	5.95	5.05	4.20	4.05	3.40	4.10	2.30	2.30	2.75	2.05	1.85
	# S2	7.10	6.20	6.80	5.35	5.90	4.90	4.15	3.95	3.40	4.05	2.20	2.05	2.85	1.95	1.85
	% S1 by S2	0.89	0.88	0.92	0.96	0.93	0.98	0.97	1.00	1.00	0.97	0.62	0.67	0.80	0.88	0.77
	% S2 by S1	0.89	0.89	0.95	0.99	0.92	0.96	0.87	0.98	0.99	0.88	0.71	0.89	0.92	0.99	0.99
pCNV < 0.05 or pCNVbaf < 0.05	# S1	6.15	5.50	5.60	4.95	5.35	4.50	3.85	3.65	3.15	3.75	1.65	1.65	1.95	1.80	1.60
	# S2	6.05	5.40	5.55	4.95	5.35	4.35	3.60	3.45	3.10	3.55	1.70	1.80	2.10	1.85	1.80
	% S1 by S2	0.94	0.94	0.98	0.98	0.95	0.98	0.96	1.00	1.00	0.97	0.82	0.87	0.92	0.93	0.87
	% S2 by S1	0.96	0.94	0.98	0.99	0.94	1.00	0.92	0.98	0.99	0.91	0.85	0.99	0.99	0.99	0.99
pCNVIrr < 0.05 or pCNVbaf < 0.05	# S1	7.35	6.50	6.80	5.45	5.95	5.05	4.20	4.05	3.40	4.10	2.30	2.30	2.75	2.05	1.85
	# S2	7.10	6.20	6.85	5.35	5.90	4.90	4.15	3.95	3.40	4.05	2.20	2.05	2.90	1.95	1.85
	% S1 by S2	0.89	0.88	0.92	0.96	0.93	0.98	0.97	1.00	1.00	0.97	0.62	0.67	0.80	0.88	0.77
	% S2 by S1	0.89	0.89	0.95	0.99	0.92	0.96	0.87	0.98	0.99	0.88	0.71	0.89	0.92	0.99	0.99
pCNV < 0.05 or pCNVIrr < 0.05 or pCNVbaf < 0.05	# S1	7.35	6.50	6.80	5.45	5.95	5.05	4.20	4.05	3.40	4.10	2.30	2.30	2.75	2.05	1.85
	# S2	7.10	6.20	6.85	5.35	5.90	4.90	4.15	3.95	3.40	4.05	2.20	2.05	2.90	1.95	1.85
	% S1 by S2	0.89	0.88	0.92	0.96	0.93	0.98	0.97	1.00	1.00	0.97	0.62	0.67	0.80	0.88	0.77
	% S2 by S1	0.89	0.89	0.95	0.99	0.92	0.96	0.87	0.98	0.99	0.88	0.71	0.89	0.92	0.99	0.99

Table S3. Concordance rate of short CNV calls between duplicate samples genotyped with Affymetrix array.

CNVision cutoff	115 duplicate pairs	Affymetrix Short Deletions (<100 kb)									
		CNVision	PennCNV	PennCNV + QuantiSNP	PennCNV + Birdsuite	QuantiSNP	QuantiSNP + PennCNV	QuantiSNP + Birdsuite	Birdsuite	Birdsuite + QuantiSNP	Birdsuite + PennCNV
No filtering	# S1	10.35	9.29	8.83	8.57	9.27	8.59	8.51	16.52	9.32	8.56
	# S2	10.25	9.37	8.93	8.73	9.09	8.45	8.49	16.81	9.36	8.57
	% S1 by S2	0.77	0.78	0.80	0.81	0.83	0.85	0.86	0.92	0.95	0.95
	% S2 by S1	0.80	0.82	0.84	0.84	0.85	0.88	0.87	0.92	0.96	0.97
pCNV<0.05	# S1	8.84	8.13	7.90	7.58	8.31	7.92	7.77	7.91	7.58	7.32
	# S2	8.57	8.01	7.80	7.57	8.12	7.79	7.67	7.50	7.29	7.06
	% S1 by S2	0.81	0.82	0.83	0.84	0.85	0.86	0.87	0.95	0.96	0.96
	% S2 by S1	0.84	0.86	0.87	0.87	0.87	0.89	0.89	0.97	0.97	0.97
pCNVlrr<0.05	# S1	9.75	8.90	8.52	8.21	8.82	8.33	8.16	8.93	8.33	7.93
	# S2	9.64	8.97	8.66	8.41	8.70	8.27	8.17	9.01	8.29	7.90
	% S1 by S2	0.78	0.78	0.80	0.81	0.83	0.85	0.85	0.94	0.95	0.95
	% S2 by S1	0.81	0.83	0.84	0.85	0.86	0.88	0.87	0.95	0.96	0.97
pCNVbaf<0.05	# S1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.02	0.01	0.01
	# S2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	% S1 by S2	NA	NA	NA	NA	NA	NA	NA	0.50	1.00	1.00
	% S2 by S1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
pCNV<0.05 or pCNVlrr<0.05	# S1	9.75	8.90	8.52	8.21	8.82	8.33	8.16	8.93	8.33	7.93
	# S2	9.64	8.97	8.66	8.41	8.70	8.27	8.17	9.01	8.29	7.90
	% S1 by S2	0.78	0.78	0.80	0.81	0.83	0.85	0.85	0.94	0.95	0.95
	% S2 by S1	0.81	0.83	0.84	0.85	0.86	0.88	0.87	0.95	0.96	0.97
pCNV<0.05 or pCNVbaf<0.05	# S1	8.84	8.13	7.90	7.58	8.31	7.92	7.77	7.92	7.59	7.33
	# S2	8.57	8.01	7.80	7.57	8.12	7.79	7.67	7.50	7.29	7.06
	% S1 by S2	0.81	0.82	0.83	0.84	0.85	0.86	0.87	0.95	0.96	0.96
	% S2 by S1	0.84	0.86	0.87	0.87	0.87	0.89	0.89	0.97	0.97	0.97
pCNVlrr<0.05 or pCNVbaf<0.05	# S1	9.75	8.90	8.52	8.21	8.82	8.33	8.16	8.94	8.34	7.94
	# S2	9.64	8.97	8.66	8.41	8.70	8.27	8.17	9.01	8.29	7.90
	% S1 by S2	0.78	0.78	0.80	0.81	0.83	0.85	0.85	0.94	0.95	0.95
	% S2 by S1	0.81	0.83	0.84	0.85	0.86	0.88	0.87	0.95	0.96	0.97
pCNV<0.05 or pCNVlrr<0.05 or pCNVbaf<0.05	# S1	9.75	8.90	8.52	8.21	8.82	8.33	8.16	8.94	8.34	7.94
	# S2	9.64	8.97	8.66	8.41	8.70	8.27	8.17	9.01	8.29	7.90
	% S1 by S2	0.78	0.78	0.80	0.81	0.83	0.85	0.85	0.94	0.95	0.95
	% S2 by S1	0.81	0.83	0.84	0.85	0.86	0.88	0.87	0.95	0.96	0.97

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CNVision cutoff	115 duplicate pairs	Affymetrix Short Duplications (<100 kb)									
		CNVision	PennCNV	PennCNV + QuantiSNP	PennCNV + Birdsuite	QuantiSNP	QuantiSNP + PennCNV	QuantiSNP + Birdsuite	Birdsuite	Birdsuite + QuantiSNP	Birdsuite + PennCNV
No filtering	# S1	6.20	5.10	4.68	2.22	5.69	4.65	2.34	2.69	1.54	1.39
	# S2	6.42	5.01	4.70	2.17	5.77	4.66	2.63	2.70	1.51	1.30
	% S1 by S2	0.69	0.65	0.67	0.71	0.73	0.77	0.79	0.80	0.90	0.91
	% S2 by S1	0.66	0.68	0.70	0.72	0.71	0.73	0.75	0.77	0.95	0.97
pCNV<0.05	# S1	1.01	0.90	0.85	0.78	0.97	0.91	0.82	0.79	0.74	0.72
	# S2	0.90	0.88	0.83	0.77	0.89	0.83	0.77	0.65	0.63	0.63
	% S1 by S2	0.76	0.80	0.81	0.84	0.80	0.82	0.84	0.89	0.91	0.93
	% S2 by S1	0.85	0.82	0.82	0.80	0.90	0.90	0.92	0.93	0.93	0.93
pCNVlrr<0.05	# S1	4.53	3.93	3.70	1.63	4.37	3.79	1.70	1.31	1.19	1.16
	# S2	4.53	3.81	3.67	1.60	4.33	3.75	1.85	1.23	1.14	1.06
	% S1 by S2	0.69	0.67	0.67	0.73	0.73	0.76	0.78	0.89	0.91	0.91
	% S2 by S1	0.66	0.68	0.69	0.68	0.72	0.75	0.73	0.93	0.94	0.95
pCNVbaf<0.05	# S1	0.57	0.52	0.50	0.45	0.52	0.49	0.45	0.47	0.43	0.43
	# S2	0.50	0.50	0.47	0.45	0.47	0.45	0.44	0.44	0.43	0.43
	% S1 by S2	0.88	0.84	0.83	0.89	0.87	0.88	0.88	0.91	0.92	0.94
	% S2 by S1	0.91	0.81	0.81	0.81	0.94	0.94	0.94	0.96	0.96	0.96
pCNV<0.05 or pCNVlrr<0.05	# S1	4.70	4.06	3.79	1.74	4.50	3.90	1.81	1.45	1.31	1.26
	# S2	4.67	3.95	3.80	1.72	4.46	3.87	1.97	1.34	1.24	1.16
	% S1 by S2	0.70	0.67	0.68	0.74	0.74	0.76	0.79	0.89	0.91	0.92
	% S2 by S1	0.68	0.68	0.69	0.69	0.74	0.76	0.75	0.94	0.95	0.96
pCNV<0.05 or pCNVbaf<0.05	# S1	1.03	0.92	0.87	0.79	0.98	0.93	0.83	0.79	0.74	0.72
	# S2	0.93	0.90	0.84	0.77	0.90	0.83	0.78	0.65	0.63	0.63
	% S1 by S2	0.75	0.80	0.81	0.84	0.80	0.82	0.84	0.89	0.91	0.93
	% S2 by S1	0.85	0.82	0.82	0.80	0.90	0.90	0.92	0.93	0.93	0.93
pCNVlrr<0.05 or pCNVbaf<0.05	# S1	4.70	4.06	3.81	1.74	4.50	3.90	1.80	1.43	1.30	1.24
	# S2	4.69	3.96	3.80	1.71	4.46	3.86	1.97	1.33	1.23	1.15
	% S1 by S2	0.70	0.68	0.68	0.75	0.74	0.77	0.79	0.89	0.91	0.92
	% S2 by S1	0.67	0.68	0.69	0.69	0.73	0.76	0.75	0.93	0.95	0.96
pCNV<0.05 or pCNVlrr<0.05 or pCNVbaf<0.05	# S1	4.73	4.08	3.81	1.75	4.51	3.91	1.82	1.45	1.31	1.26
	# S2	4.70	3.97	3.81	1.72	4.47	3.87	1.98	1.34	1.24	1.16
	% S1 by S2	0.70	0.67	0.68	0.74	0.74	0.77	0.79	0.89	0.91	0.92
	% S2 by S1	0.68	0.68	0.69	0.69	0.74	0.76	0.75	0.94	0.95	0.96

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CNVision cutoff	115 duplicate pairs	Affymetrix All Short CNVs (<100 kb)									
		CNVision	PennCNV	PennCNV + QuantiSNP	PennCNV + Birdsuite	QuantiSNP	QuantiSNP + PennCNV	QuantiSNP + Birdsuite	Birdsuite	Birdsuite + QuantiSNP	Birdsuite + PennCNV
No filtering	# S1	16.55	14.38	13.50	10.78	14.96	13.24	10.85	19.21	10.86	9.95
	# S2	16.67	14.37	13.63	10.90	14.86	13.11	11.11	19.50	10.87	9.87
	% S1 by S2	0.74	0.73	0.75	0.78	0.79	0.82	0.84	0.90	0.95	0.95
	% S2 by S1	0.74	0.76	0.78	0.81	0.79	0.82	0.84	0.90	0.95	0.96
pCNV<0.05	# S1	9.85	9.03	8.75	8.37	9.28	8.83	8.58	8.70	8.32	8.04
	# S2	9.47	8.89	8.63	8.33	9.01	8.63	8.44	8.15	7.92	7.70
	% S1 by S2	0.81	0.82	0.83	0.84	0.84	0.86	0.86	0.94	0.96	0.96
	% S2 by S1	0.84	0.85	0.86	0.87	0.88	0.89	0.89	0.96	0.96	0.97
pCNVIrr<0.05	# S1	14.28	12.83	12.22	9.84	13.18	12.12	9.85	10.24	9.52	9.09
	# S2	14.17	12.77	12.33	10.01	13.03	12.02	10.03	10.24	9.43	8.96
	% S1 by S2	0.75	0.75	0.76	0.80	0.79	0.81	0.83	0.93	0.95	0.95
	% S2 by S1	0.76	0.78	0.79	0.83	0.81	0.83	0.85	0.95	0.96	0.96
pCNVbaf<0.05	# S1	0.57	0.52	0.50	0.45	0.52	0.49	0.45	0.49	0.44	0.43
	# S2	0.50	0.50	0.47	0.45	0.47	0.45	0.44	0.44	0.43	0.43
	% S1 by S2	0.88	0.84	0.83	0.89	0.87	0.88	0.88	0.89	0.92	0.94
	% S2 by S1	0.91	0.81	0.81	0.81	0.94	0.94	0.94	0.96	0.96	0.96
pCNV<0.05 or pCNVIrr<0.05	# S1	14.45	12.97	12.31	9.95	13.31	12.23	9.97	10.38	9.64	9.19
	# S2	14.31	12.91	12.46	10.13	13.16	12.14	10.15	10.35	9.53	9.05
	% S1 by S2	0.75	0.75	0.76	0.80	0.80	0.82	0.84	0.94	0.95	0.95
	% S2 by S1	0.76	0.78	0.79	0.82	0.81	0.83	0.85	0.95	0.96	0.96
pCNV<0.05 or pCNVbaf<0.05	# S1	9.88	9.05	8.77	8.37	9.30	8.85	8.59	8.71	8.33	8.05
	# S2	9.50	8.90	8.64	8.33	9.02	8.63	8.45	8.15	7.92	7.70
	% S1 by S2	0.81	0.82	0.83	0.84	0.84	0.86	0.86	0.94	0.96	0.96
	% S2 by S1	0.84	0.85	0.86	0.87	0.88	0.89	0.89	0.96	0.96	0.97
pCNVIrr<0.05 or pCNVbaf<0.05	# S1	14.45	12.97	12.33	9.95	13.31	12.23	9.96	10.37	9.63	9.18
	# S2	14.33	12.92	12.46	10.12	13.16	12.13	10.15	10.34	9.52	9.04
	% S1 by S2	0.75	0.75	0.76	0.80	0.80	0.82	0.84	0.94	0.95	0.95
	% S2 by S1	0.76	0.78	0.79	0.82	0.81	0.83	0.85	0.95	0.96	0.96
pCNV<0.05 or pCNVIrr<0.05 or pCNVbaf<0.05	# S1	14.48	12.98	12.33	9.96	13.33	12.24	9.97	10.39	9.65	9.20
	# S2	14.34	12.93	12.47	10.13	13.17	12.14	10.16	10.35	9.53	9.05
	% S1 by S2	0.75	0.75	0.76	0.80	0.80	0.82	0.84	0.94	0.95	0.95
	% S2 by S1	0.76	0.78	0.79	0.82	0.81	0.83	0.85	0.95	0.96	0.96

Table S4. Concordance rate of long CNV calls between duplicate samples genotyped with Affymetrix array.

CNVision cutoff	115 duplicate pairs	Affymetrix Long Deletions (>100 kb)									
		CNVision	PennCNV	PennCNV + QuantiSNP	PennCNV + Birdsuite	QuantiSNP	QuantiSNP + PennCNV	QuantiSNP + Birdsuite	Birdsuite	Birdsuite + QuantiSNP	Birdsuite + PennCNV
No filtering	# S1	2.14	2.07	1.96	1.84	1.85	1.81	1.67	3.58	1.80	1.85
	# S2	2.12	2.08	1.96	1.83	1.91	1.90	1.68	3.65	1.82	1.85
	% S1 by S2	0.84	0.88	0.90	0.91	0.90	0.90	0.91	0.93	0.95	0.96
	% S2 by S1	0.85	0.87	0.89	0.90	0.90	0.89	0.91	0.90	0.94	0.95
pCNV<0.05	# S1	1.67	1.60	1.56	1.48	1.52	1.51	1.39	1.37	1.32	1.36
	# S2	1.58	1.54	1.50	1.42	1.53	1.53	1.40	1.43	1.40	1.43
	% S1 by S2	0.92	0.97	0.97	0.98	0.93	0.93	0.94	0.99	0.99	0.99
	% S2 by S1	0.91	0.94	0.95	0.97	0.95	0.95	0.97	0.99	0.99	0.99
pCNVIrr<0.05	# S1	1.92	1.82	1.74	1.67	1.66	1.65	1.52	1.61	1.52	1.57
	# S2	1.92	1.89	1.81	1.70	1.77	1.77	1.59	1.74	1.61	1.67
	% S1 by S2	0.87	0.92	0.93	0.94	0.91	0.91	0.92	0.97	0.99	0.98
	% S2 by S1	0.89	0.90	0.91	0.93	0.90	0.90	0.92	0.98	0.98	0.98
pCNVbaf<0.05	# S1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	# S2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	% S1 by S2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	% S2 by S1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
pCNV<0.05 or pCNVIrr<0.05	# S1	1.92	1.82	1.74	1.67	1.66	1.65	1.52	1.61	1.52	1.57
	# S2	1.92	1.89	1.81	1.70	1.77	1.77	1.59	1.74	1.61	1.67
	% S1 by S2	0.87	0.92	0.93	0.94	0.91	0.91	0.92	0.97	0.99	0.98
	% S2 by S1	0.89	0.90	0.91	0.93	0.90	0.90	0.92	0.98	0.98	0.98
pCNV<0.05 or pCNVbaf<0.05	# S1	1.67	1.60	1.56	1.48	1.52	1.51	1.39	1.37	1.32	1.36
	# S2	1.58	1.54	1.50	1.42	1.53	1.53	1.40	1.43	1.40	1.43
	% S1 by S2	0.92	0.97	0.97	0.98	0.93	0.93	0.94	0.99	0.99	0.99
	% S2 by S1	0.91	0.94	0.95	0.97	0.95	0.95	0.97	0.99	0.99	0.99
pCNVIrr<0.05 or pCNVbaf<0.05	# S1	1.92	1.82	1.74	1.67	1.66	1.65	1.52	1.61	1.52	1.57
	# S2	1.92	1.89	1.81	1.70	1.77	1.77	1.59	1.74	1.61	1.67
	% S1 by S2	0.87	0.92	0.93	0.94	0.91	0.91	0.92	0.97	0.99	0.98
	% S2 by S1	0.89	0.90	0.91	0.93	0.90	0.90	0.92	0.98	0.98	0.98
pCNV<0.05 or pCNVIrr<0.05 or pCNVbaf<0.05	# S1	1.92	1.82	1.74	1.67	1.66	1.65	1.52	1.61	1.52	1.57
	# S2	1.92	1.89	1.81	1.70	1.77	1.77	1.59	1.74	1.61	1.67
	% S1 by S2	0.87	0.92	0.93	0.94	0.91	0.91	0.92	0.97	0.99	0.98
	% S2 by S1	0.89	0.90	0.91	0.93	0.90	0.90	0.92	0.98	0.98	0.98

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CNVision cutoff	115 duplicate pairs	Affymetrix Long Duplications (>100 kb)									
		CNVision	PennCNV	PennCNV + QuantiSNP	PennCNV + Birdsuite	QuantiSNP	QuantiSNP + PennCNV	QuantiSNP + Birdsuite	Birdsuite	Birdsuite + QuantiSNP	Birdsuite + PennCNV
No filtering	# S1	3.23	3.17	2.74	1.93	2.70	2.62	1.70	2.99	1.46	1.58
	# S2	3.57	3.56	3.17	2.19	2.98	2.85	1.83	3.10	1.62	1.71
	% S1 by S2	0.75	0.81	0.86	0.87	0.83	0.84	0.88	0.83	0.93	0.93
	% S2 by S1	0.73	0.75	0.79	0.78	0.77	0.80	0.81	0.80	0.92	0.92
pCNV<0.05	# S1	0.76	0.74	0.74	0.69	0.75	0.75	0.69	0.63	0.63	0.63
	# S2	0.77	0.75	0.75	0.65	0.75	0.75	0.66	0.62	0.62	0.62
	% S1 by S2	0.95	0.97	0.97	0.97	0.98	0.98	0.97	1.00	1.00	1.00
	% S2 by S1	0.94	0.96	0.96	1.00	0.96	0.96	0.98	1.00	1.00	1.00
pCNVlrr<0.05	# S1	2.16	2.25	2.06	1.37	2.02	2.01	1.28	1.15	1.09	1.12
	# S2	2.25	2.26	2.20	1.37	2.17	2.13	1.33	1.12	1.12	1.12
	% S1 by S2	0.83	0.87	0.89	0.90	0.86	0.86	0.89	0.97	0.97	0.97
	% S2 by S1	0.83	0.86	0.87	0.87	0.82	0.84	0.86	0.92	0.92	0.92
pCNVbaf<0.05	# S1	0.44	0.45	0.44	0.44	0.45	0.45	0.44	0.43	0.42	0.43
	# S2	0.44	0.43	0.43	0.43	0.42	0.42	0.41	0.41	0.40	0.41
	% S1 by S2	0.95	1.00	1.00	1.00	0.95	0.95	0.95	1.00	1.00	1.00
	% S2 by S1	0.96	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
pCNV<0.05 or pCNVlrr<0.05	# S1	2.23	2.32	2.13	1.44	2.09	2.08	1.35	1.22	1.16	1.19
	# S2	2.35	2.36	2.30	1.47	2.25	2.22	1.42	1.22	1.22	1.22
	% S1 by S2	0.83	0.87	0.90	0.91	0.86	0.86	0.89	0.97	0.98	0.98
	% S2 by S1	0.84	0.86	0.87	0.88	0.83	0.84	0.87	0.93	0.93	0.93
pCNV<0.05 or pCNVbaf<0.05	# S1	0.77	0.77	0.76	0.71	0.77	0.77	0.70	0.65	0.64	0.65
	# S2	0.78	0.77	0.76	0.67	0.75	0.75	0.66	0.63	0.63	0.63
	% S1 by S2	0.93	0.97	0.97	0.97	0.98	0.98	0.97	1.00	1.00	1.00
	% S2 by S1	0.94	0.96	0.96	1.00	0.96	0.96	0.98	1.00	1.00	1.00
pCNVlrr<0.05 or pCNVbaf<0.05	# S1	2.24	2.35	2.15	1.47	2.10	2.10	1.37	1.23	1.17	1.21
	# S2	2.36	2.37	2.30	1.48	2.25	2.22	1.42	1.23	1.23	1.23
	% S1 by S2	0.83	0.88	0.90	0.91	0.86	0.86	0.89	0.97	0.98	0.98
	% S2 by S1	0.84	0.86	0.87	0.88	0.83	0.84	0.87	0.93	0.93	0.93
pCNV<0.05 or pCNVlrr<0.05 or pCNVbaf<0.05	# S1	2.24	2.35	2.15	1.47	2.10	2.10	1.37	1.23	1.17	1.21
	# S2	2.37	2.37	2.30	1.49	2.25	2.22	1.42	1.23	1.23	1.23
	% S1 by S2	0.83	0.88	0.90	0.91	0.86	0.86	0.89	0.97	0.98	0.98
	% S2 by S1	0.84	0.86	0.87	0.88	0.83	0.84	0.87	0.93	0.93	0.93

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CNVision cutoff	115 duplicate pairs	Affymetrix All Long CNVs (>100 kb)									
		CNVision	PennCNV	PennCNV + QuantiSNP	PennCNV + Birdsuite	QuantiSNP	QuantiSNP + PennCNV	QuantiSNP + Birdsuite	Birdsuite	Birdsuite + QuantiSNP	Birdsuite + PennCNV
No filtering	# S1	5.37	5.24	4.70	3.77	4.56	4.43	3.37	6.57	3.26	3.43
	# S2	5.69	5.63	5.13	4.02	4.90	4.75	3.50	6.76	3.43	3.57
	% S1 by S2	0.79	0.83	0.87	0.89	0.86	0.87	0.90	0.88	0.93	0.94
	% S2 by S1	0.75	0.78	0.81	0.82	0.81	0.83	0.86	0.85	0.92	0.93
pCNV<0.05	# S1	2.43	2.34	2.30	2.17	2.27	2.26	2.08	2.00	1.96	1.99
	# S2	2.35	2.29	2.24	2.07	2.28	2.28	2.06	2.05	2.02	2.05
	% S1 by S2	0.92	0.97	0.97	0.97	0.94	0.94	0.95	0.99	0.99	0.99
	% S2 by S1	0.92	0.94	0.95	0.98	0.96	0.96	0.98	0.99	0.99	0.99
pCNVIrr<0.05	# S1	4.08	4.07	3.80	3.04	3.68	3.66	2.80	2.76	2.61	2.69
	# S2	4.17	4.15	4.01	3.08	3.94	3.90	2.92	2.86	2.73	2.79
	% S1 by S2	0.85	0.89	0.91	0.93	0.89	0.90	0.92	0.97	0.98	0.97
	% S2 by S1	0.85	0.86	0.86	0.89	0.84	0.85	0.89	0.96	0.96	0.96
pCNVbaf<0.05	# S1	0.44	0.45	0.44	0.44	0.45	0.45	0.44	0.43	0.42	0.43
	# S2	0.44	0.43	0.43	0.43	0.42	0.42	0.41	0.41	0.40	0.41
	% S1 by S2	0.95	1.00	1.00	1.00	0.95	0.95	0.95	1.00	1.00	1.00
	% S2 by S1	0.96	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
pCNV<0.05 or pCNVIrr<0.05	# S1	4.15	4.14	3.87	3.11	3.75	3.73	2.87	2.83	2.68	2.76
	# S2	4.27	4.24	4.10	3.17	4.03	3.98	3.01	2.96	2.83	2.89
	% S1 by S2	0.85	0.89	0.91	0.93	0.90	0.90	0.92	0.97	0.98	0.97
	% S2 by S1	0.85	0.86	0.87	0.90	0.85	0.86	0.89	0.96	0.96	0.96
pCNV<0.05 or pCNVbaf<0.05	# S1	2.44	2.37	2.31	2.19	2.29	2.28	2.10	2.02	1.97	2.01
	# S2	2.37	2.30	2.25	2.09	2.28	2.28	2.06	2.07	2.03	2.07
	% S1 by S2	0.91	0.97	0.97	0.97	0.94	0.94	0.95	0.99	0.99	0.99
	% S2 by S1	0.92	0.94	0.95	0.98	0.96	0.96	0.98	0.99	0.99	0.99
pCNVIrr<0.05 or pCNVbaf<0.05	# S1	4.17	4.17	3.89	3.14	3.77	3.75	2.89	2.84	2.69	2.77
	# S2	4.28	4.25	4.10	3.18	4.03	3.98	3.01	2.97	2.83	2.90
	% S1 by S2	0.85	0.90	0.91	0.93	0.90	0.90	0.92	0.97	0.98	0.97
	% S2 by S1	0.85	0.86	0.87	0.90	0.85	0.86	0.89	0.96	0.96	0.96
pCNV<0.05 or pCNVIrr<0.05 or pCNVbaf<0.05	# S1	4.17	4.17	3.89	3.14	3.77	3.75	2.89	2.84	2.69	2.77
	# S2	4.29	4.26	4.11	3.19	4.03	3.98	3.01	2.97	2.83	2.90
	% S1 by S2	0.85	0.90	0.91	0.93	0.90	0.90	0.92	0.97	0.98	0.97
	% S2 by S1	0.85	0.86	0.87	0.90	0.85	0.86	0.89	0.96	0.96	0.96

Table S5. Concordance rate of short CNV calls between duplicate samples genotyped with Illumina array.

CNVision cutoff	20 duplicate pairs	Illumina All CNVs (<100 kb)					Illumina Deletions (<100 kb)					Illumina Duplications (<100 kb)				
		CNVision	PennCNV	QuantiSNP	QuantiSNP + PennCNV	PennCNV + QuantiSNP	CNVision	PennCNV	QuantiSNP	QuantiSNP + PennCNV	PennCNV + QuantiSNP	CNVision	PennCNV	QuantiSNP	QuantiSNP + PennCNV	PennCNV + QuantiSNP
No filtering	# S1	6.30	5.70	4.90	4.05	4.85	4.95	4.10	3.40	2.90	3.75	1.35	1.60	1.50	1.15	1.10
	# S2	6.00	5.45	4.60	4.00	4.70	4.85	4.10	3.35	2.95	3.60	1.15	1.35	1.25	1.05	1.10
	% S1 by S2	0.87	0.89	0.94	0.98	0.95	0.95	0.95	1.00	1.00	0.97	0.57	0.67	0.79	0.90	0.83
	% S2 by S1	0.89	0.86	0.93	0.95	0.93	0.94	0.88	0.93	0.94	0.92	0.72	0.79	0.92	1.00	0.92
pCNV < 0.05	# S1	3.90	3.75	3.45	3.05	3.65	3.15	2.95	2.60	2.25	2.90	0.75	0.80	0.85	0.80	0.75
	# S2	3.90	3.60	3.50	3.10	3.55	3.10	2.65	2.45	2.15	2.60	0.80	0.95	1.05	0.95	0.95
	% S1 by S2	0.96	0.92	1.00	1.00	0.93	0.99	0.93	1.00	1.00	0.93	0.82	0.91	1.00	1.00	1.00
	% S2 by S1	0.97	0.95	0.98	0.99	0.95	1.00	0.94	0.97	0.99	0.94	0.86	1.00	1.00	1.00	1.00
pCNVIrr < 0.05	# S1	4.80	4.40	3.80	3.25	3.95	3.65	3.30	2.90	2.50	3.25	1.15	1.10	0.90	0.75	0.70
	# S2	4.65	4.15	3.75	3.20	3.85	3.60	3.15	2.85	2.45	3.05	1.05	1.00	0.90	0.75	0.80
	% S1 by S2	0.91	0.90	0.96	0.97	0.95	0.99	0.96	1.00	1.00	0.96	0.60	0.65	0.78	0.80	0.89
	% S2 by S1	0.90	0.87	0.97	0.99	0.92	0.95	0.88	0.97	0.99	0.91	0.80	0.85	0.91	1.00	1.00
pCNVbaf < 0.05	# S1	0.60	0.65	0.75	0.70	0.65	0.00	0.00	0.00	0.00	0.00	0.60	0.65	0.75	0.70	0.65
	# S2	0.70	0.85	0.95	0.85	0.85	0.00	0.00	0.00	0.00	0.00	0.70	0.85	0.95	0.85	0.85
	% S1 by S2	0.89	1.00	1.00	1.00	1.00	NA	NA	NA	NA	NA	0.89	1.00	1.00	1.00	1.00
	% S2 by S1	0.83	1.00	1.00	1.00	1.00	NA	NA	NA	NA	NA	0.83	1.00	1.00	1.00	1.00
pCNV < 0.05 or pCNVIrr < 0.05	# S1	4.90	4.60	4.05	3.45	4.15	3.65	3.30	2.90	2.50	3.25	1.25	1.30	1.15	0.95	0.90
	# S2	4.70	4.30	4.00	3.40	4.00	3.60	3.15	2.85	2.45	3.05	1.10	1.15	1.15	0.95	0.95
	% S1 by S2	0.91	0.90	0.96	0.97	0.95	0.99	0.96	1.00	1.00	0.96	0.63	0.72	0.83	0.86	0.91
	% S2 by S1	0.90	0.88	0.97	0.99	0.93	0.95	0.88	0.97	0.99	0.91	0.74	0.87	0.92	1.00	1.00
pCNV < 0.05 or pCNVbaf < 0.05	# S1	3.90	3.75	3.45	3.05	3.65	3.15	2.95	2.60	2.25	2.90	0.75	0.80	0.85	0.80	0.75
	# S2	3.90	3.60	3.50	3.10	3.55	3.10	2.65	2.45	2.15	2.60	0.80	0.95	1.05	0.95	0.95
	% S1 by S2	0.96	0.92	1.00	1.00	0.93	0.99	0.93	1.00	1.00	0.93	0.82	0.91	1.00	1.00	1.00
	% S2 by S1	0.97	0.95	0.98	0.99	0.95	1.00	0.94	0.97	0.99	0.94	0.86	1.00	1.00	1.00	1.00
pCNVIrr < 0.05 or pCNVbaf < 0.05	# S1	4.90	4.60	4.05	3.45	4.15	3.65	3.30	2.90	2.50	3.25	1.25	1.30	1.15	0.95	0.90
	# S2	4.70	4.30	4.00	3.40	4.00	3.60	3.15	2.85	2.45	3.05	1.10	1.15	1.15	0.95	0.95
	% S1 by S2	0.91	0.90	0.96	0.97	0.95	0.99	0.96	1.00	1.00	0.96	0.63	0.72	0.83	0.86	0.91
	% S2 by S1	0.90	0.88	0.97	0.99	0.93	0.95	0.88	0.97	0.99	0.91	0.74	0.87	0.92	1.00	1.00
pCNV < 0.05 or pCNVIrr < 0.05 or pCNVbaf < 0.05	# S1	4.90	4.60	4.05	3.45	4.15	3.65	3.30	2.90	2.50	3.25	1.25	1.30	1.15	0.95	0.90
	# S2	4.70	4.30	4.00	3.40	4.00	3.60	3.15	2.85	2.45	3.05	1.10	1.15	1.15	0.95	0.95
	% S1 by S2	0.90	0.91	0.96	0.97	0.95	0.99	0.96	1.00	1.00	0.96	0.63	0.69	0.83	0.86	0.91
	% S2 by S1	0.89	0.87	0.97	0.99	0.92	0.95	0.88	0.97	0.99	0.92	0.74	0.86	0.92	1.00	1.00

Table S6. Concordance rate of long CNV calls between duplicate samples genotyped with Illumina array.

CNVision cutoff	20 duplicate pairs	Illumina All CNVs (>100 kb)					Illumina Deletions (>100 kb)					Illumina Duplications (>100 kb)				
		CNVision	PennCNV	QuantiSNP	QuantiSNP + PennCNV	PennCNV + QuantiSNP	CNVision	PennCNV	QuantiSNP	QuantiSNP + PennCNV	PennCNV + QuantiSNP	CNVision	PennCNV	QuantiSNP	QuantiSNP + PennCNV	PennCNV + QuantiSNP
No filtering	# S1	2.65	2.00	3.20	2.10	1.85	1.45	0.90	1.20	0.90	0.85	1.20	1.10	2.00	1.20	1.00
	# S2	2.70	2.15	3.20	2.00	2.05	1.50	1.15	1.20	1.00	1.15	1.20	1.00	2.00	1.00	0.90
	% S1 by S2	0.83	0.79	0.81	0.93	0.83	0.95	0.92	1.00	1.00	1.00	0.68	0.68	0.69	0.89	0.73
	% S2 by S1	0.82	0.86	0.92	0.99	0.91	0.85	0.87	1.00	1.00	0.87	0.73	0.88	0.85	0.97	0.95
pCNV < 0.05	# S1	2.25	1.75	2.15	1.90	1.70	1.35	0.90	1.05	0.90	0.85	0.90	0.85	1.10	1.00	0.85
	# S2	2.15	1.80	2.00	1.85	1.80	1.25	0.95	1.00	0.95	0.95	0.90	0.85	1.00	0.90	0.85
	% S1 by S2	0.89	0.84	0.93	0.95	0.86	0.97	0.92	1.00	1.00	1.00	0.77	0.77	0.88	0.92	0.77
	% S2 by S1	0.92	0.92	0.99	0.99	0.92	1.00	0.86	1.00	1.00	0.86	0.83	0.95	0.97	0.97	0.95
pCNVIrr < 0.05	# S1	2.35	1.80	2.55	1.85	1.70	1.40	0.90	1.15	0.90	0.85	0.95	0.90	1.40	0.95	0.85
	# S2	2.15	1.70	2.55	1.70	1.70	1.30	1.00	1.10	0.95	1.00	0.85	0.70	1.45	0.75	0.70
	% S1 by S2	0.84	0.80	0.89	0.95	0.83	0.95	0.92	1.00	1.00	1.00	0.63	0.63	0.83	0.92	0.68
	% S2 by S1	0.93	0.90	0.94	0.98	0.90	0.98	0.86	1.00	1.00	0.86	0.75	0.94	0.87	0.96	0.94
pCNVbaf < 0.05	# S1	0.70	0.70	0.90	0.80	0.70	0.00	0.00	0.00	0.00	0.00	0.70	0.70	0.90	0.80	0.70
	# S2	0.80	0.75	0.85	0.75	0.75	0.00	0.00	0.00	0.00	0.00	0.80	0.75	0.85	0.75	0.75
	% S1 by S2	0.90	0.90	0.96	1.00	0.90	NA	NA	NA	NA	NA	0.90	0.90	0.96	1.00	0.90
	% S2 by S1	0.86	1.00	1.00	1.00	1.00	NA	NA	NA	NA	NA	0.86	1.00	1.00	1.00	1.00
pCNV < 0.05 or pCNVIrr < 0.05	# S1	2.45	1.90	2.75	2.00	1.80	1.40	0.90	1.15	0.90	0.85	1.05	1.00	1.60	1.10	0.95
	# S2	2.40	1.90	2.80	1.95	1.90	1.30	1.00	1.10	0.95	1.00	1.10	0.90	1.70	1.00	0.90
	% S1 by S2	0.84	0.80	0.87	0.95	0.83	0.95	0.92	1.00	1.00	1.00	0.67	0.67	0.82	0.93	0.71
	% S2 by S1	0.88	0.91	0.94	0.99	0.91	0.98	0.86	1.00	1.00	0.86	0.73	0.95	0.89	0.97	0.95
pCNV < 0.05 or pCNVbaf < 0.05	# S1	2.25	1.75	2.15	1.90	1.70	1.35	0.90	1.05	0.90	0.85	0.90	0.85	1.10	1.00	0.85
	# S2	2.15	1.80	2.05	1.85	1.80	1.25	0.95	1.00	0.95	0.95	0.90	0.85	1.05	0.90	0.85
	% S1 by S2	0.89	0.84	0.93	0.95	0.86	0.97	0.92	1.00	1.00	1.00	0.77	0.77	0.88	0.92	0.77
	% S2 by S1	0.92	0.92	0.99	0.99	0.92	1.00	0.86	1.00	1.00	0.86	0.83	0.95	0.97	0.97	0.95
pCNVIrr < 0.05 or pCNVbaf < 0.05	# S1	2.45	1.90	2.75	2.00	1.80	1.40	0.90	1.15	0.90	0.85	1.05	1.00	1.60	1.10	0.95
	# S2	2.40	1.90	2.85	1.95	1.90	1.30	1.00	1.10	0.95	1.00	1.10	0.90	1.75	1.00	0.90
	% S1 by S2	0.84	0.80	0.87	0.95	0.83	0.95	0.92	1.00	1.00	1.00	0.67	0.67	0.82	0.93	0.71
	% S2 by S1	0.88	0.91	0.94	0.99	0.91	0.98	0.86	1.00	1.00	0.86	0.73	0.95	0.90	0.97	0.95
pCNV < 0.05 or pCNVIrr < 0.05 or pCNVbaf < 0.05	# S1	2.45	1.90	2.75	2.00	1.80	1.40	0.90	1.15	0.90	0.85	1.05	1.00	1.60	1.10	0.95
	# S2	2.40	1.90	2.85	1.95	1.90	1.30	1.00	1.10	0.95	1.00	1.10	0.90	1.75	1.00	0.90
	% S1 by S2	0.83	0.82	0.87	0.94	0.88	0.95	0.91	1.00	1.00	1.00	0.64	0.64	0.82	0.92	0.77
	% S2 by S1	0.88	0.91	0.94	0.99	0.91	0.98	0.85	1.00	1.00	0.86	0.71	0.95	0.90	0.97	0.95

Table S7. Global CNV burden analyses by permutation tests.

A. Deletions

Type of Del	Type of CNV	Tested effect	All (<1%)			Singleton CNVs			> 500 kb CNVs			> 1 Mb CNVs		
			Cases	Controls	p value	Cases	Controls	p value	Cases	Controls	p value	Cases	Controls	p value
Long (> 100 kb or longer)	All	CNVs/subj	0.3242	0.3181	1.82E-01	0.0559	0.0501	8.10E-02	0.0216	0.0189	2.06E-01	0.0066	0.0044	9.41E-02
		Subjs w CNV	0.2818	0.2709	4.49E-02	0.0547	0.0485	6.59E-02	0.0215	0.0186	1.90E-01	0.0066	0.0044	9.41E-02
	Intergenic	CNVs/subj	0.1337	0.1376	6.31E-01	0.0206	0.0180	1.09E-01	0.0028	0.0020	3.97E-01	0.0010	0.0003	1.16E-01
		Subjs w CNV	0.1247	0.1298	7.16E-01	0.0204	0.0178	1.15E-01	0.0028	0.0020	3.97E-01	0.0010	0.0003	1.16E-01
	Gene-containing	CNVs/subj	0.1905	0.1805	7.12E-02	0.0420	0.0376	1.38E-01	0.0189	0.0169	2.39E-01	0.0055	0.0041	1.99E-01
		Subjs w CNV	0.1773	0.1628	1.05E-02	0.0412	0.0370	1.52E-01	0.0189	0.0166	2.00E-01	0.0055	0.0041	1.99E-01
		Genes/CNV	0.7183	0.7074	3.75E-01	0.1294	0.1420	7.78E-01	0.2097	0.1656	1.08E-01	0.0931	0.0457	4.65E-02
		Genes/CNV kb	0.0099	0.0098	5.26E-01	0.0120	0.0131	8.92E-01	0.0113	0.0116	3.72E-01	0.0100	0.0079	1.66E-01
	Exon-containing	CNVs/subj	0.1754	0.1683	1.04E-01	0.0410	0.0364	1.14E-01	0.0189	0.0169	2.42E-01	0.0055	0.0041	1.98E-01
		Subjs w CNV	0.1635	0.1532	3.00E-02	0.0403	0.0358	1.20E-01	0.0189	0.0166	2.04E-01	0.0055	0.0041	1.98E-01
		Genes/CNV	3.8760	3.6940	2.74E-01	0.6983	0.7495	7.04E-01	1.3940	1.0450	6.54E-02	0.6121	0.3052	5.56E-02
		Genes/CNV kb	0.0477	0.0468	4.62E-01	0.0586	0.0673	9.18E-01	0.0742	0.0727	2.58E-01	0.0639	0.0525	2.02E-01
	Intronic	CNVs/subj	0.0151	0.0122	2.07E-01	0.0036	0.0027	3.55E-01	0.0000	0.0000	1.00E+00	0.0000	0.0000	1.00E+00
		Subjs w CNV	0.0151	0.0119	1.70E-01	0.0036	0.0027	3.55E-01	0.0000	0.0000	1.00E+00	0.0000	0.0000	1.00E+00
Short (< 100 kb)	All	CNVs/subj	1.0150	0.9777	2.20E-03	0.2154	0.2009	3.30E-02						
		Subjs w CNV	0.5798	0.5744	1.87E-02	0.1865	0.1719	5.35E-03						
	Intergenic	CNVs/subj	0.5062	0.4831	4.03E-03	0.1048	0.0921	6.90E-03						
		Subjs w CNV	0.3692	0.3651	5.31E-02	0.0972	0.0868	1.01E-02						
	Gene-containing	CNVs/subj	0.5087	0.4946	6.21E-02	0.1176	0.1155	3.03E-01						
		Subjs w CNV	0.3791	0.3684	2.07E-02	0.1059	0.1049	3.14E-01						
		Genes/CNV	0.8919	0.8518	3.55E-02	0.2109	0.1947	1.50E-01						
		Genes/CNV kb	0.0281	0.0286	6.02E-01	0.0329	0.0346	6.85E-01						
	Exon-containing	CNVs/subj	0.3299	0.3097	2.99E-02	0.0893	0.0851	2.52E-01						
		Subjs w CNV	0.2697	0.2522	5.55E-03	0.0808	0.0782	3.01E-01						
		Genes/CNV	2.1270	1.9440	5.15E-02	0.5422	0.5066	3.49E-01						
		Genes/CNV kb	0.0558	0.0535	3.14E-01	0.0670	0.0685	7.92E-01						
	Intronic	CNVs/subj	0.1787	0.1849	4.91E-01	0.0351	0.0386	7.09E-01						
		Subjs w CNV	0.1616	0.1641	3.22E-01	0.0337	0.0377	7.47E-01						

(continues on next page)

B. Duplications

Type of Dup	Type of CNV	Tested effect	All (< 1%)			Singleton CNVs			> 500 kb CNVs			> 1 Mb CNVs		
			Cases	Controls	p value	Cases	Controls	p value	Cases	Controls	p value	Cases	Controls	p value
Long (> 100 kb or longer)	All	CNVs/subj	0.4960	0.4763	1.18E-01	0.0863	0.0753	3.16E-02	0.0720	0.0712	6.49E-01	0.0161	0.0155	5.99E-01
		Subjs w CNV	0.3678	0.3630	4.09E-01	0.0779	0.0700	6.29E-02	0.0678	0.0684	7.35E-01	0.0157	0.0152	6.00E-01
	Intergenic	CNVs/subj	0.0867	0.0791	9.35E-02	0.0225	0.0184	7.17E-02	0.0076	0.0066	4.14E-01	0.0012	0.0005	1.74E-01
		Subjs w CNV	0.0818	0.0747	1.06E-01	0.0218	0.0180	7.37E-02	0.0076	0.0066	4.14E-01	0.0012	0.0005	1.74E-01
	Gene-containing	CNVs/subj	0.4093	0.3972	2.20E-01	0.0702	0.0651	2.11E-01	0.0644	0.0646	6.92E-01	0.0149	0.0151	7.04E-01
		Subjs w CNV	0.3161	0.3129	4.32E-01	0.0633	0.0614	4.17E-01	0.0614	0.0620	7.15E-01	0.0145	0.0148	7.09E-01
		Genes/CNV	2.4920	2.5020	5.27E-01	0.2901	0.2750	4.60E-01	0.7848	0.8495	7.81E-01	0.3318	0.3714	7.38E-01
		Genes/CNV kb	0.0172	0.0181	9.41E-01	0.0161	0.0171	8.48E-01	0.0122	0.0131	6.64E-01	0.0130	0.0137	5.28E-01
	Exon-containing	CNVs/subj	0.4057	0.3948	2.47E-01	0.0694	0.0647	2.44E-01	0.0644	0.0646	6.91E-01	0.0149	0.0151	7.08E-01
		Subjs w CNV	0.3135	0.3118	5.08E-01	0.0628	0.0611	4.32E-01	0.0614	0.0620	7.13E-01	0.0145	0.0148	7.13E-01
		Genes/CNV	15.3200	15.0900	4.12E-01	1.6930	1.6330	5.53E-01	5.4280	5.9070	7.69E-01	2.3660	2.6810	7.37E-01
		Genes/CNV kb	0.0954	0.0961	5.93E-01	0.0889	0.0957	8.91E-01	0.0846	0.0889	5.62E-01	0.0922	0.0997	5.50E-01
	Intronic	CNVs/subj	0.0036	0.0024	1.02E-01	0.0017	0.0012	2.86E-01	0.0000	0.0000	1.00E+00	0.0000	0.0000	1.00E+00
		Subjs w CNV	0.0036	0.0024	1.02E-01	0.0017	0.0012	2.86E-01	0.0000	0.0000	1.00E+00	0.0000	0.0000	1.00E+00
Short (< 100 kb)	All	CNVs/subj	0.6702	0.7015	7.80E-01	0.1715	0.1773	6.21E-01						
		Subjs w CNV	0.4616	0.4582	1.24E-01	0.1517	0.1471	1.17E-01						
	Intergenic	CNVs/subj	0.2524	0.2655	7.32E-01	0.0706	0.0696	2.29E-01						
		Subjs w CNV	0.2164	0.2199	3.59E-01	0.0677	0.0628	4.89E-02						
	Gene-containing	CNVs/subj	0.4178	0.4360	7.22E-01	0.1069	0.1133	8.21E-01						
		Subjs w CNV	0.3237	0.3189	1.48E-01	0.0965	0.0978	5.40E-01						
		Genes/CNV	0.9334	0.9953	8.76E-01	0.2285	0.2372	6.74E-01						
		Genes/CNV kb	0.0339	0.0334	4.64E-01	0.0326	0.0338	7.50E-01						
	Exon-containing	CNVs/subj	0.3446	0.3645	8.29E-01	0.0898	0.0973	8.93E-01						
		Subjs w CNV	0.2756	0.2748	3.36E-01	0.0815	0.0845	7.22E-01						
		Genes/CNV	3.5150	3.6340	7.19E-01	0.8014	0.8504	7.56E-01						
		Genes/CNV kb	0.1089	0.1020	1.78E-01	0.0937	0.1027	9.13E-01						
	Intronic	CNVs/subj	0.0732	0.0715	2.28E-01	0.0192	0.0220	8.13E-01						
		Subjs w CNV	0.0701	0.0667	1.16E-01	0.0190	0.0217	8.09E-01						

Shown are results of global burden analyses of deletions and of duplications in cases vs. controls for all CNVs in each class (genic, exonic, intronic and intergenic CNVs) and then separately for CNVs < 100 kb and > 100 kb, with secondary analyses for singleton CNVs (occurring only once in this entire dataset), CNVs > 500 kb and CNVs > 1000 kb. All tests are one-sided permutations based on the assumption of increased CNV burden in cases. CNVs/subj, average number of CNVs per subject; Subjs w CNV, proportion of subjects with at least one CNV; Genes/CNV, number of genes spanned per CNV; Genes/CNV kb, number of genes per total CNV kb.

Table S8. Results of multiple linear regressions.

A. Deletions

Type of Deletion	Type of CNV	Tested effect	All (<1%)		Singleton CNVs		>500kb CNVs		>1Mb CNVs	
			NSEG p value	KB p value	NSEG p value	KB p value	NSEG p value	KB p value	NSEG p value	KB p value
Long (>100kb)	All	Sex	6.49E-01	5.86E-01	5.42E-01	4.95E-01	3.71E-01	2.04E-01	3.87E-01	1.56E-01
		Phenotype	4.84E-01	3.66E-01	1.92E-01	6.93E-01	3.55E-01	2.20E-01	1.26E-01	2.10E-01
		Batch	6.29E-07	4.66E-04	8.77E-07	3.74E-06	2.83E-01	3.92E-01	1.91E-01	1.67E-01
	Gene-containing	Sex	6.76E-01	5.28E-01	2.36E-01	2.56E-01	6.91E-01	3.61E-01	5.20E-01	2.10E-01
		Phenotype	2.17E-01	2.75E-01	2.97E-01	5.53E-01	4.52E-01	3.44E-01	2.81E-01	3.68E-01
		Batch	4.69E-04	2.30E-02	1.88E-07	8.42E-08	1.44E-01	5.39E-01	2.73E-01	3.56E-01
	Exon-containing	Sex	8.91E-01	6.78E-01	3.25E-01	2.58E-01	6.91E-01	3.61E-01	5.20E-01	2.10E-01
		Phenotype	3.15E-01	3.12E-01	2.50E-01	4.30E-01	4.52E-01	3.44E-01	2.81E-01	3.68E-01
		Batch	2.90E-03	5.16E-02	1.48E-07	2.08E-07	1.44E-01	5.39E-01	2.73E-01	3.56E-01
	Intronic	Sex	4.36E-02	6.38E-02	2.09E-01	1.79E-01	NA	NA	NA	NA
		Phenotype	3.28E-01	4.58E-01	4.94E-01	9.14E-01	NA	NA	NA	NA
		Batch	7.73E-03	1.77E-03	2.19E-01	1.90E-01	NA	NA	NA	NA
	Intergenic	Sex	2.35E-01	9.63E-01	4.47E-01	6.55E-01	1.25E-01	1.85E-01	4.50E-01	4.52E-01
		Phenotype	7.10E-01	8.67E-01	2.21E-01	4.45E-01	5.17E-01	2.80E-01	1.35E-01	1.74E-01
		Batch	1.32E-04	5.79E-05	5.73E-02	4.51E-01	3.65E-02	3.84E-02	2.97E-02	5.32E-02
Short (<100kb)	All	Sex	2.27E-04	1.91E-02	1.21E-01	7.20E-01				
		Phenotype	2.28E-01	5.04E-02	2.25E-01	4.29E-02				
		Batch	0.00E+00	1.59E-161	3.81E-68	1.82E-22				
	Gene-containing	Sex	5.15E-03	9.24E-03	4.41E-01	3.85E-01				
		Phenotype	6.34E-01	1.64E-01	8.82E-01	2.97E-01				
		Batch	1.11E-208	5.36E-69	6.77E-34	9.57E-10				
	Exon-containing	Sex	1.19E-03	1.22E-03	3.38E-01	4.22E-01				
		Phenotype	2.41E-01	7.38E-02	6.46E-01	2.88E-01				
		Batch	6.30E-120	7.74E-44	4.24E-22	1.11E-06				
	Intronic	Sex	7.66E-01	6.20E-01	7.17E-01	9.56E-01				
		Phenotype	3.83E-01	7.08E-01	3.41E-01	8.23E-01				
		Batch	3.41E-109	2.29E-31	4.80E-20	7.64E-06				
	Intergenic	Sex	9.42E-03	5.37E-01	1.10E-01	6.51E-01				
		Phenotype	1.83E-01	1.39E-01	4.95E-02	3.70E-02				
		Batch	4.67E-316	1.52E-113	2.96E-49	6.21E-18				

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B. Duplications

Type of Duplication	Type of CNV	Tested effect	All (<1%)		Singleton CNVs		>500kb CNVs		>1Mb CNVs	
			NSEG p value	KB p value	NSEG p value	KB p value	NSEG p value	KB p value	NSEG p value	KB p value
Long (>100kb)	All	Sex	6.80E-01	3.61E-01	5.20E-01	1.77E-01	1.34E-01	1.11E-01	3.53E-01	3.10E-01
		Phenotype	2.11E-01	4.63E-01	5.80E-02	2.48E-01	8.91E-01	8.37E-01	9.50E-01	7.03E-01
		Batch	5.58E-04	9.13E-08	1.02E-03	7.19E-04	1.86E-07	1.45E-08	1.29E-04	4.34E-05
	Gene-containing	Sex	5.07E-01	4.16E-01	3.07E-01	6.86E-02	1.80E-01	2.10E-01	4.05E-01	4.58E-01
		Phenotype	4.47E-01	8.51E-01	4.01E-01	9.17E-01	7.56E-01	7.83E-01	7.96E-01	8.16E-01
		Batch	9.30E-04	6.35E-05	1.02E-02	2.52E-03	7.21E-07	1.24E-05	3.10E-03	2.18E-02
	Exon-containing	Sex	5.06E-01	4.26E-01	3.59E-01	1.20E-01	1.80E-01	2.10E-01	4.05E-01	4.58E-01
		Phenotype	5.01E-01	8.67E-01	4.52E-01	9.67E-01	7.56E-01	7.83E-01	7.96E-01	8.16E-01
		Batch	1.06E-03	6.87E-05	7.90E-03	4.11E-03	7.21E-07	1.24E-05	3.10E-03	2.18E-02
	Intronic	Sex	9.89E-01	6.67E-01	6.86E-01	5.53E-01	NA	NA	NA	NA
		Phenotype	2.07E-01	6.31E-01	4.85E-01	4.58E-01	NA	NA	NA	NA
		Batch	8.96E-01	7.82E-01	5.92E-01	5.93E-01	NA	NA	NA	NA
	Intergenic	Sex	5.70E-01	6.46E-01	7.38E-01	8.21E-01	4.54E-01	2.20E-01	6.04E-01	3.80E-01
		Phenotype	1.15E-01	1.09E-01	1.28E-01	2.44E-01	6.10E-01	1.90E-01	1.58E-01	1.06E-01
		Batch	1.70E-05	1.10E-08	1.43E-02	2.10E-02	5.38E-03	6.70E-07	1.51E-04	3.28E-07
Short (<100kb)	All	Sex	3.77E-01	1.78E-01	2.73E-01	3.59E-01				
		Phenotype	1.29E-01	2.66E-01	6.41E-01	9.75E-01				
		Batch	1.01E-160	1.31E-57	3.90E-31	2.94E-12				
	Gene-containing	Sex	3.68E-01	2.64E-01	9.79E-01	9.75E-01				
		Phenotype	2.70E-01	5.89E-01	3.27E-01	7.49E-01				
		Batch	1.15E-89	2.44E-27	1.42E-20	5.05E-07				
	Exon-containing	Sex	4.68E-01	3.38E-01	6.01E-01	7.24E-01				
		Phenotype	1.61E-01	4.40E-01	1.80E-01	5.15E-01				
		Batch	5.74E-77	1.72E-24	1.78E-18	2.98E-06				
	Intronic	Sex	4.76E-01	3.95E-01	1.41E-01	2.43E-01				
		Phenotype	6.33E-01	4.40E-01	4.09E-01	5.49E-01				
		Batch	1.11E-26	1.47E-08	7.18E-03	3.04E-01				
	Intergenic	Sex	7.17E-01	3.89E-01	9.45E-02	1.15E-01				
		Phenotype	2.03E-01	1.72E-01	6.02E-01	5.31E-01				
		Batch	4.39E-110	4.36E-46	2.13E-16	1.62E-07				

Shown are results of multiple linear regressions to evaluate the potential confounding effect by using total CNV number or length as dependent variable and case/control status, batch, and sex as independent variables. Analyses were conducted separately for deletions and duplications, for longer and shorter (<100kb) CNVs, for all CNVs, and those overlapping with at least one gene, and those overlapping with at least one exon. Only rare CNVs were used. P values surviving FDR correction (< 0.05) are in red.

Table S9. Global burden analyses of CNVs in down-sampled dataset.

A. Deletions

Type of Del	Type of CNV	Tested effect	All (< 1%)			Singleton CNVs			> 500 kb CNVs			> 1 Mb CNVs		
			Cases	Controls	p value	Cases	Controls	p value	Cases	Controls	p value	Cases	Controls	p value
Long (> 100 kb or longer)	All	CNVs/subj	0.3283	0.3101	1.00E-01	0.0829	0.0768	2.03E-01	0.0225	0.0210	3.68E-01	0.0062	0.0049	3.07E-01
		Subjs w CNV	0.2851	0.2626	2.27E-02	0.0798	0.0728	1.51E-01	0.0222	0.0207	3.67E-01	0.0062	0.0049	3.07E-01
	Intergenic	CNVs/subj	0.1332	0.1338	5.42E-01	0.0324	0.0296	2.88E-01	0.0022	0.0025	6.96E-01	0.0012	0.0000	6.30E-02
		Subjs w CNV	0.1245	0.1270	6.34E-01	0.0321	0.0287	2.35E-01	0.0022	0.0025	6.96E-01	0.0012	0.0000	6.30E-02
	Gene-containing	CNVs/subj	0.1951	0.1763	4.16E-02	0.0604	0.0536	1.38E-01	0.0204	0.0185	3.28E-01	0.0049	0.0049	5.69E-01
		Subjs w CNV	0.1809	0.1600	1.37E-02	0.0586	0.0524	1.53E-01	0.0204	0.0182	2.93E-01	0.0049	0.0049	5.69E-01
		Genes/CNV	0.7793	0.7226	2.38E-01	0.1637	0.1936	8.28E-01	0.2549	0.1899	1.54E-01	0.1174	0.0647	1.26E-01
		Genes/CNV kb	0.0102	0.0097	2.14E-01	0.0103	0.0106	6.00E-01	0.0131	0.0119	3.33E-01	0.0131	0.0098	1.87E-01
	Exon-containing	CNVs/subj	0.1825	0.1649	4.75E-02	0.0583	0.0515	1.31E-01	0.0204	0.0185	3.25E-01	0.0049	0.0049	5.71E-01
		Subjs w CNV	0.1699	0.1510	2.15E-02	0.0570	0.0506	1.35E-01	0.0204	0.0182	2.91E-01	0.0049	0.0049	5.71E-01
		Genes/CNV	4.2240	3.7410	1.80E-01	0.9041	0.9439	5.91E-01	1.6740	1.1740	1.24E-01	0.7380	0.4405	1.82E-01
		Genes/CNV kb	0.0493	0.0453	1.78E-01	0.0519	0.0520	5.00E-01	0.0856	0.0711	2.25E-01	0.0797	0.0663	3.20E-01
	Intronic	CNVs/subj	0.0126	0.0114	3.70E-01	0.0049	0.0052	6.34E-01	0.0000	0.0000	1.00E+00	0.0000	0.0000	1.00E+00
		Subjs w CNV	0.0126	0.0108	2.81E-01	0.0049	0.0052	6.34E-01	0.0000	0.0000	1.00E+00	0.0000	0.0000	1.00E+00
Short (< 100 kb)	All	CNVs/subj	0.9846	0.9202	8.95E-03	0.2965	0.2700	6.13E-02						
		Subjs w CNV	0.5746	0.5524	2.81E-02	0.2432	0.2260	4.86E-02						
	Intergenic	CNVs/subj	0.4867	0.4562	3.77E-02	0.1430	0.1292	7.23E-02						
		Subjs w CNV	0.3634	0.3471	7.40E-02	0.1307	0.1190	7.92E-02						
	Gene-containing	CNVs/subj	0.4978	0.4639	4.62E-02	0.1603	0.1470	1.74E-01						
		Subjs w CNV	0.3739	0.3502	2.10E-02	0.1381	0.1344	3.42E-01						
		Genes/CNV	0.8711	0.7879	2.53E-02	0.2855	0.2401	6.11E-02						
		Genes/CNV kb	0.0275	0.0272	4.05E-01	0.0315	0.0318	5.45E-01						
	Exon-containing	CNVs/subj	0.3227	0.2925	3.24E-02	0.1190	0.1054	1.33E-01						
		Subjs w CNV	0.2636	0.2426	2.55E-02	0.1039	0.0996	2.99E-01						
		Genes/CNV	2.1170	1.7490	9.85E-03	0.7472	0.5530	2.59E-02						
		Genes/CNV kb	0.0549	0.0523	2.40E-01	0.0620	0.0591	3.47E-01						
	Intronic	CNVs/subj	0.1751	0.1714	3.72E-01	0.0487	0.0484	5.04E-01						
		Subjs w CNV	0.1591	0.1535	2.76E-01	0.0466	0.0469	5.50E-01						

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B. Duplications

Type of Dup	Type of CNV	Tested effect	All (< 1%)			Singleton CNVs			> 500 kb CNVs			> 1 Mb CNVs		
			Cases	Controls	p value	Cases	Controls	p value	Cases	Controls	p value	Cases	Controls	p value
Long (> 100 kb or longer)	All	CNVs/subj	0.4790	0.5003	8.50E-01	0.1178	0.1264	8.29E-01	0.0678	0.0731	7.96E-01	0.0160	0.0179	7.48E-01
		Subjs w CNV	0.3607	0.3721	8.35E-01	0.1054	0.1134	8.60E-01	0.0638	0.0700	8.53E-01	0.0157	0.0176	7.54E-01
	Intergenic	CNVs/subj	0.0823	0.0839	6.00E-01	0.0299	0.0277	3.31E-01	0.0071	0.0068	4.98E-01	0.0009	0.0006	5.02E-01
		Subjs w CNV	0.0768	0.0792	6.61E-01	0.0290	0.0268	3.24E-01	0.0071	0.0068	4.98E-01	0.0009	0.0006	5.02E-01
	Gene-containing	CNVs/subj	0.3967	0.4165	8.52E-01	0.0946	0.1067	9.23E-01	0.0607	0.0663	8.22E-01	0.0151	0.0173	7.82E-01
		Subjs w CNV	0.3132	0.3187	6.92E-01	0.0848	0.0983	9.74E-01	0.0583	0.0632	8.11E-01	0.0148	0.0170	7.89E-01
		Genes/CNV	2.5020	2.7340	8.34E-01	0.3995	0.5000	9.46E-01	0.8086	0.9695	8.65E-01	0.3708	0.4454	7.39E-01
		Genes/CNV kb	0.0179	0.0178	4.16E-01	0.0153	0.0176	9.50E-01	0.0127	0.0141	8.25E-01	0.0140	0.0139	4.94E-01
	Exon-containing	CNVs/subj	0.3930	0.4137	8.64E-01	0.0928	0.1057	9.41E-01	0.0607	0.0663	8.23E-01	0.0151	0.0173	7.80E-01
		Subjs w CNV	0.3110	0.3172	7.12E-01	0.0835	0.0977	9.79E-01	0.0583	0.0632	8.11E-01	0.0148	0.0170	7.86E-01
		Genes/CNV	15.2500	16.7100	8.14E-01	2.2780	2.9420	9.56E-01	5.6890	6.8400	8.67E-01	2.6820	3.2410	7.49E-01
		Genes/CNV kb	0.0989	0.0955	2.41E-01	0.0809	0.0979	9.80E-01	0.0902	0.0978	7.61E-01	0.1015	0.1025	5.21E-01
	Intronic	CNVs/subj	0.0037	0.0028	3.29E-01	0.0022	0.0015	3.88E-01	0.0000	0.0000	1.00E+00	0.0000	0.0000	1.00E+00
		Subjs w CNV	0.0037	0.0028	3.29E-01	0.0022	0.0015	3.88E-01	0.0000	0.0000	1.00E+00	0.0000	0.0000	1.00E+00
Short (< 100 kb)	All	CNVs/subj	0.6510	0.6609	6.63E-01	0.2263	0.2420	8.69E-01						
		Subjs w CNV	0.4553	0.4448	1.99E-01	0.1924	0.1961	6.59E-01						
	Intergenic	CNVs/subj	0.2478	0.2408	3.00E-01	0.0925	0.0863	2.27E-01						
		Subjs w CNV	0.2118	0.2065	3.10E-01	0.0863	0.0798	1.84E-01						
	Gene-containing	CNVs/subj	0.4032	0.4202	8.17E-01	0.1384	0.1618	9.82E-01						
		Subjs w CNV	0.3200	0.3113	2.32E-01	0.1224	0.1335	9.16E-01						
		Genes/CNV	0.9084	0.9701	8.63E-01	0.3110	0.3419	8.55E-01						
		Genes/CNV kb	0.0328	0.0325	4.18E-01	0.0332	0.0342	6.56E-01						
	Exon-containing	CNVs/subj	0.3332	0.3499	8.37E-01	0.1181	0.1359	9.64E-01						
		Subjs w CNV	0.2731	0.2673	3.07E-01	0.1057	0.1147	8.82E-01						
		Genes/CNV	3.5310	3.6040	6.07E-01	1.1200	1.1820	6.81E-01						
		Genes/CNV kb	0.1120	0.1001	2.89E-02	0.1018	0.1026	5.27E-01						
	Intronic	CNVs/subj	0.0700	0.0703	5.36E-01	0.0219	0.0290	9.66E-01						
		Subjs w CNV	0.0681	0.0650	3.25E-01	0.0210	0.0284	9.77E-01						

Shown are results of global burden analysis on down-sampled dataset consisting of 6,488 subjects in which there were equal number of male cases, male controls, female cases and female controls within each cohort.

Table S10. Manually checked genes and regions with stratified permutation test and CMH test P < 0.01.

A. Deletions in genes (exonic)

Gene	Chr	Start	End	Comb_Case	Comb_Cont	EMP p-value	CMH OR	CMH p-value	RADIANT case	RADIANT Cont	GR Illum case	GR Illum Cont	GR Affy case	GR Affy Cont	Neth case	Neth Cont	Plot check	RADIANT cov	GR Illum cov	Affy cov	Rare region	Prop test p-value	VALID
PASSED QC																							
MSR1	8	15,965,386	16,050,300	55	32	2.05E-03	1.96	1.93E-03	23	10	6	3	15	10	11	9	+	Y	Y	Y	Y	5.68E-02	Y
FAILED QC																							
NEU4	2	242,750,159	242,758,739	12	2	4.59E-03	6.53	4.89E-03	12	2	0	0	0	0	0	0	+	Y	Y	Y	N	1.38E-04	N
LOC93622	4	6,675,820	6,677,774	25	3	7.00E-05	7.60	6.96E-05	0	0	25	3	0	0	0	0	-	Y	Y	Y	Y	8.65E-39	N
PRKN	6	161,768,589	163,148,834	29	16	1.63E-02	2.03	1.72E-02	15	9	3	3	4	2	7	2	+	Y	Y	Y	Y	3.44E-01	N
LOC441242	7	64,600,748	65,235,797	7	0	4.55E-03	Inf	4.34E-03	1	0	0	0	3	0	3	0	+	Y	Y	Y	N	1.60E-01	N
PEMT	17	17,408,876	17,495,017	16	0	2.00E-05	Inf	1.20E-05	16	0	0	0	0	0	0	0	-	Y	Y	Y	Y	3.40E-05	N

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B. Duplications in genes (exonic)

Gene	Chr	Start	End	Comb_Case	Comb_Cont	EMP p-value	CMH OR	CMH p-value	RADIANT case	RADIANT Cont	GR Illum case	GR Illum Cont	GR Affy case	GR Affy Cont	Neth case	Neth Cont	Plot check	RADIANT cov	GR Illum cov	GR Affy cov	Rare region	Prop test p-value	VALID
PASSED QC																							
TUBGCP5	15	22,833,394	22,873,891	24	7	7.80E-04	3.88	7.58E-04	7	3	11	0	2	1	4	3	+	Y	Y	Y	Y	2.32E-03	Y
CYFIP1	15	22,892,648	23,003,603	24	7	7.80E-04	3.88	7.58E-04	7	3	11	0	2	1	4	3	+	Y	Y	Y	Y	4.28E-03	Y
NIPA2	15	23,004,683	23,034,427	24	7	8.60E-04	3.88	7.58E-04	7	3	11	0	2	1	4	3	+	Y	Y	Y	Y	4.28E-03	Y
NIPA1	15	23,043,278	23,086,843	24	7	6.70E-04	3.88	7.58E-04	7	3	11	0	2	1	4	3	+	Y	Y	Y	Y	4.28E-03	Y
FAILED QC																							
NBPF1	1	16,888,921	16,940,100	54	40	9.07E-03	1.70	8.21E-03	0	0	5	1	11	15	38	24	+	N	Y	Y	N	1.26E-20	N
CROCCP2	1	16,944,750	16,957,401	57	41	4.22E-03	1.77	4.17E-03	0	0	5	1	12	15	40	25	+	N	Y	Y	N	9.36E-22	N
TM4SF20	2	228,226,873	228,244,022	91	63	2.73E-03	1.67	2.68E-03	1	0	90	63	0	0	0	0	+	Low	Y	Low	N	2.59E-213	N
HLA-DQA1	6	32,605,182	32,611,429	25	10	7.30E-03	2.69	7.09E-03	0	1	25	9	0	0	0	0	-	Low	Y	Low	N	2.18E-45	N
PRH1-PRR4	12	10,998,447	11,324,224	31	13	4.72E-03	2.53	4.36E-03	0	0	31	12	0	0	0	1	?	Low	Y	Y	N	6.05E-58	N
PRH1	12	11,033,559	11,324,222	31	13	4.21E-03	2.53	4.36E-03	0	0	31	12	0	0	0	1	?	Low	Y	Y	N	6.05E-58	N
TAS2R46	12	11,213,963	11,214,893	31	12	2.58E-03	2.74	2.59E-03	0	0	31	12	0	0	0	0	?	Low	Y	Y	N	1.03E-59	N
TAS2R43	12	11,243,885	11,244,912	31	12	2.69E-03	2.74	2.59E-03	0	0	31	12	0	0	0	0	?	Low	Y	Y	N	1.03E-59	N
RASA3	13	114,747,193	114,898,095	30	9	2.00E-04	3.81	1.65E-04	26	8	1	1	3	0	0	0	-	Y	Y	Y	Y	7.37E-08	N
ZFYVE1	14	73,436,152	73,493,920	3	0	3.86E-02	Inf	3.98E-02	1	0	0	0	1	0	1	0	+	Y	Y	Y	Y	8.30E-01	N
ASPG	14	104,552,022	104,579,046	24	3	8.00E-05	7.63	5.24E-05	23	3	0	0	0	0	1	0	+	Y	Y	Low	Y	1.38E-07	N
MIR203A	14	104,583,741	104,583,851	24	3	8.00E-05	7.63	5.24E-05	23	3	0	0	0	0	1	0	+	Y	Y	Low	Y	1.38E-07	N
MIR203B	14	104,583,754	104,583,840	24	3	5.00E-05	7.63	5.24E-05	23	3	0	0	0	0	1	0	+	Y	Y	Low	Y	1.38E-07	N
KIF26A	14	104,605,059	104,647,235	23	3	1.20E-04	7.26	9.69E-05	23	3	0	0	0	0	0	0	+	Y	Y	Low	Y	2.84E-08	N
GOLGA8DP	15	22,702,284	22,715,728	9	1	8.34E-03	10.36	8.25E-03	0	0	6	0	2	0	1	1	+	Y	Y	Y	Y	1.41E-04	N
GOLGA6L1	15	22,736,245	22,746,002	9	1	8.80E-03	10.36	8.25E-03	0	0	6	0	2	0	1	1	+	Y	Y	Y	Y	1.41E-04	N
GOLGA6L22	15	22,736,267	22,746,002	9	1	8.04E-03	10.36	8.25E-03	0	0	6	0	2	0	1	1	+	Y	Y	Y	Y	1.41E-04	N
LOC283683	15	23,094,330	23,115,254	24	6	4.10E-04	4.49	3.56E-04	7	2	11	0	2	1	4	3	+	Y	Y	Y	Y	2.79E-03	N
WHAMMP3	15	23,187,728	23,208,357	20	5	8.70E-04	4.59	9.93E-04	4	1	11	0	2	1	3	3	+	Y	Y	Y	Y	1.31E-04	N
HERC2P2	15	23,282,264	23,378,259	13	3	4.80E-03	5.33	4.88E-03	0	0	9	0	2	1	2	2	+	Y	Y	Y	Y	3.13E-06	N
ERVV-1	19	53,517,343	53,519,833	85	66	5.71E-03	1.59	5.92E-03	4	3	80	61	0	1	1	1	+	Y	Y	Y	N	5.40E-181	N
LILRB3	19	54,720,146	54,746,711	77	47	4.70E-04	1.95	3.92E-04	20	7	48	33	6	3	3	4	+	Y	Y	Y	N	9.74E-63	N
TPTE	21	10,906,186	10,990,943	60	29	1.00E-05	3.30	2.46E-07	0	0	3	4	57	25	0	0	-	N	Y	Y	N	5.94E-74	N

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C. Deletions in CNV regions

Region	Comb Case	Comb cont	EMP p-value	CMH OR	CMH p-value	RADIANT case	RADIANT cont	GR Affy case	GR Affy cont	GR Illum case	GR Illum cont	Neth case	Neth cont	Plot check	RADIANT cov	Affy cov	GR Illum cov	Rare region	Prop test p-value	VALID
PASSED QC																				
chr6:162,136,159-163,489,668	65	40	8.90E-04	1.92	9.74E-04	33	17	10	11	9	5	13	7	+	Y	Y	Y	Y	2.02E-01	Y
chr6:162,177,023-163,489,668	65	40	9.50E-04	1.92	9.74E-04	33	17	10	11	9	5	13	7	+	Y	Y	Y	Y	2.02E-01	Y
chr6:162,804,504-164,033,649	55	35	3.66E-03	1.84	3.63E-03	26	11	9	10	8	4	12	10	+	Y	Y	Y	Y	8.02E-01	Y
chr8:15,817,196-16,045,585	58	33	9.50E-04	2.03	9.74E-04	24	10	17	11	6	3	11	9	+	Y	Y	Y	Y	1.15E-02	Y
chr8:15,817,196-16,092,656	59	33	8.10E-04	2.05	7.45E-04	24	10	18	11	6	3	11	9	+	Y	Y	Y	Y	6.03E-03	Y
FAILED QC																				
chr1:106,307,942-106,367,506	23	2	1.00E-05	14.71	1.89E-06	0	0	0	0	20	0	3	2	-	N	Y	Y	Y	5.61E-21	N
chr1:106,327,837-106,371,203	20	0	1.00E-05	Inf	1.66E-07	0	0	0	0	20	0	0	0	-	N	Y	Y	Y	1.13E-27	N
chr2:57,270,600-57,595,408	7	0	2.82E-03	Inf	2.96E-03	2	0	1	0	2	0	2	0	+	Y	Y	Y	Y	6.86E-01	N
chr2:89,141,311-90,403,624	13	1	4.70E-04	16.51	4.25E-04	0	0	0	0	13	1	0	0	?	N	N	Y	N	2.28E-19	N
chr4:36,894,737-36,936,789	21	5	7.10E-04	4.74	7.26E-04	0	0	10	1	9	3	2	1	+	Y	Y	Y	Y	3.03E-09	N
chr4:6,618,624-6,652,800	25	5	4.70E-04	4.75	4.71E-04	0	0	0	0	25	4	0	1	-	Y	Y	Y	Y	1.93E-38	N
chr4:6,627,084-6,687,545	25	5	6.00E-04	4.75	4.71E-04	0	0	0	0	25	4	0	1	-	Y	Y	Y	Y	1.93E-38	N
chr4:186,394,634-186,421,724	14	4	5.91E-03	4.27	5.52E-03	0	0	2	2	0	0	12	2	+	Low	Y	Y	Y	1.03E-05	N
chr8:14,802,942-14,825,833	5	0	4.15E-02	Inf	4.21E-02	1	0	2	0	1	0	1	0	+	Y	Y	Y	Y	5.34E-01	N
chr15:94,779,085-94,829,625	15	6	1.27E-02	3.16	1.29E-02	10	2	1	3	2	1	2	0	+	Y	Y	Y	Y	2.61E-01	N
chr17:17,400,972-17,444,638	16	0	2.00E-05	Inf	1.20E-05	16	0	0	0	0	0	0	0	-	Y	Y	Y	Y	3.40E-05	N
chr20:14,569,942-15,082,546	84 (83)	66	6.22E-03	1.55	5.84E-03	30	19	13	13	18	13	23	21	+	Y	Y	Y	N	4.00E-02	N
chr20:14,569,942-15,100,284	84 (83)	67	7.81E-03	1.52	7.80E-03	30	20	13	13	18	13	23	21	+	Y	Y	Y	N	4.88E-02	N
chr20:14,569,942-15,170,143	84 (83)	67	8.28E-03	1.52	7.80E-03	30	20	13	13	18	13	23	21	+	Y	Y	Y	N	4.88E-02	N
chr20:14,569,942-15,107,038	84 (83)	67	8.50E-03	1.52	7.80E-03	30	20	13	13	18	13	23	21	+	Y	Y	Y	N	4.88E-02	N
chr20:14,714,457-15,234,769	80 (79)	62	6.57E-03	1.57	5.96E-03	30	20	12	12	15	13	23	17	+	Y	Y	Y	N	1.54E-01	N
chr20:14,837,263-15,254,051	66 (65)	50	8.94E-03	1.62	8.25E-03	28	17	11	9	11	10	16	14	+	Y	Y	Y	N	5.37E-01	N

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D. Duplications in CNV regions.

Region	Comb Case	Comb cont	EMP p-value	CMH OR	CMH p-value	RADIANT case	RADIANT cont	GR Affy case	GR Affy cont	GR Illum case	GR Illum cont	Neth case	Neth cont	Plot check	RADIANT cov	Affy cov	GR Illum cov	Rare region	Prop test p-value	VALID
PASSED QC																				
chr6:106,549,398-107,026,323	6	0	6.06E-03	Inf	5.93E-03	2	0	1	0	0	0	3	0	+	Y	Y	Y	Y	5.88E-01	Y
chr15:22,652,330-23,309,294	24	7	7.80E-04	3.88	7.58E-04	7	3	2	1	11	0	4	3	+	Y	Y	Y	Y	2.32E-03	Y
FAILED QC																				
chr1:188,993,946-189,828,204	19	7	9.18E-03	2.98	9.33E-03	13	2	0	1	4	3	2	1	-	Y	Y	Y	Y	1.33E-02	N
chr1:188,993,946-189,870,893	19	7	9.45E-03	2.98	9.33E-03	13	2	0	1	4	3	2	1	-	Y	Y	Y	Y	1.33E-02	N
chr4:33,223,075-33,512,554	9	1	5.17E-03	11.08	5.14E-03	9	1	0	0	0	0	0	0	-	Y	Y	Y	Y	2.20E-03	N
chr6:27,601,587-28,004,982	25	13	9.36E-03	2.38	9.48E-03	1	1	5	5	9	5	10	2	+	Y	Y	Y	Y	2.34E-06	N
chr6:27,601,587-27,985,388	25	13	9.49E-03	2.38	9.48E-03	1	1	5	5	9	5	10	2	+	Y	Y	Y	Y	2.34E-06	N
chr7:6,065,194-6,518,359	2	0	7.13E-02	Inf	7.10E-02	0	0	1	0	1	0	0	0	+	Y	Y	Y	Y	2.10E-01	N
chr9:10,412,112-11,645,495	32	18	3.87E-03	2.34	3.78E-03	3	6	27	1	0	10	2	1	-	Y	Y	Y	Y	1.64E-12	N
chr9:10,412,112-11,321,119	31	18	5.81E-03	2.24	6.05E-03	2	6	27	1	0	10	2	1	-	Y	Y	Y	Y	5.18E-13	N
chr12:129,153,544-129,581,856	20	11	3.32E-02	2.12	3.48E-02	11	6	3	3	1	1	5	1	+	Y	Y	Y	Y	3.14E-01	N
chr13:114,576,614-115,108,397	35	14	6.80E-04	2.84	5.93E-04	28	12	3	0	2	2	2	0	-	Y	Y	Y	Y	1.13E-07	N
chr13:114,610,675-115,108,397	34	10	8.00E-05	3.86	5.58E-05	27	9	3	0	2	1	2	0	-	Y	Y	Y	Y	6.65E-07	N
chr13:114,740,938-115,108,397	34	10	8.00E-05	3.86	5.58E-05	27	9	3	0	2	1	2	0	-	Y	Y	Y	Y	6.65E-07	N
chr14:104,478,511-104,640,011	24	3	6.00E-05	7.63	5.24E-05	23	3	0	0	0	0	1	0	+	Y	Low	Y	Y	1.38E-07	N
chr18:50,127,781-50,166,065	4	0	4.84E-02	Inf	4.95E-02	2	0	1	0	1	0	0	0	+	Y	Y	Y	Y	6.33E-01	N

Shown are the numbers of CNVs in each gene or CNV region for all cohorts combined and also for each cohort with CMH p < 0.01 and permutation p < 0.01 for manual review, separately for deletions and duplications. Value in parentheses is the number of individuals carrying the CNV if it is not the same number as CNVs. All tests were stratified for batch and sex. Emp p-value = empirical (permutation-based) p-values. CMH = Cochrane-Mantel-Haenszel exact tests. OR = odds ratio. Inf = infinite, OR not calculable with 0 CNVs in cases. Prop test p-value = proportion test p-values. In column RADIANT cov, Affy cov, and GR Illum cov, Y = >10 probes on the genotyping platform, N = no probes, Low = Not enough probes. In column Rare region and VALID, Y = yes, N = no. "+" represents passing plot check; "-" failed; "?" unclear.

Table S11. Summary of number of CNV calls.

Cohort	CNV type	Total CNVs	CNVs/subject	Long (>100 kb)	Long CNVs/subject	Short (<100 kb)	Short CNVs/subject
Combined cohorts	ALL	217,339	17.5189	53,133	4.2828	164,206	13.2360
	Deletions	155,636	12.5452	24,611	1.9838	131,025	10.5614
	Duplications	61,703	4.9736	28,522	2.2990	33,181	2.6746
	RARE (<1%)	30,871	2.4884	10,005	0.8065	20,866	1.6819
	Deletions	16,326	1.3160	3,982	0.3210	12,344	0.9950
	Duplications	14,545	1.1724	6,023	0.4855	8,522	0.6869
RADIANT cohort	ALL	20,402	4.0424	8,239	1.6325	12,163	2.4099
	Deletions	11,095	2.1983	2,914	0.5774	8,181	1.6210
	Duplications	9,307	1.8441	5,325	1.0551	3,982	0.7890
	RARE (<1%)	8,293	1.6432	3,906	0.7739	4,387	0.8692
	Deletions	3,721	0.7373	1,455	0.2883	2,266	0.4490
	Duplications	4,572	0.9059	2,451	0.4856	2,121	0.4202
NESDA/NTR cohort	ALL	88,641	25.4642	21,772	6.2545	66,869	19.2097
	Deletions	65,938	18.9423	9,721	2.7926	56,217	16.1497
	Duplications	22,703	6.5220	12,051	3.4619	10,652	3.0600
	RARE (<1%)	10,190	2.9273	2,917	0.8380	7,273	2.0893
	Deletions	5,700	1.6375	1,158	0.3327	4,542	1.3048
	Duplications	4,490	1.2899	1,759	0.5053	2,731	0.7845
GenRED cohort	ALL	54,841	24.8712	14,214	6.4463	40,627	18.4249
	Deletions	42,077	19.0825	8,051	3.6512	34,026	15.4313
	Duplications	12,764	5.7887	6,163	2.7950	6,601	2.9937
	RARE (<1%)	6,074	2.7546	1,705	0.7732	4,369	1.9814
	Deletions	3,471	1.5741	771	0.3497	2,700	1.2245
	Duplications	2,603	1.1805	934	0.4236	1,669	0.7569
GenRED-II cohort	ALL	53,455	31.9516	8,908	5.3246	44,547	26.6270
	Deletions	36,526	21.8326	3,925	2.3461	32,601	19.4866
	Duplications	16,929	10.1189	4,983	2.9785	11,946	7.1405
	RARE (<1%)	6,314	3.7741	1,477	0.8828	4,837	2.8912
	Deletions	3,434	2.0526	598	0.3574	2,836	1.6952
	Duplications	2,880	1.7215	879	0.5254	2,001	1.1961

Table S12. Logistic regression analyses of global burden of CNVs for each cohort.

A. Deletions

Type of Dels	Type of CNV	RADIANT (<1%)				GenRED II (<1%)				GenRED (<1%)				NESDA/NTR (<1%)			
		OR	2.50%	97.50%	p value	OR	2.50%	97.50%	p value	OR	2.50%	97.50%	p value	OR	2.50%	97.50%	p value
Long (>100kb)	All	1.0287	0.9270	1.1415	5.94E-01	1.1880	0.9973	1.4176	5.46E-02	1.0167	0.8726	1.1839	8.31E-01	0.9789	0.8712	1.0993	7.19E-01
	Genic	0.9699	0.8473	1.1096	6.57E-01	1.1486	0.9104	1.4510	2.44E-01	1.1131	0.9154	1.3530	2.82E-01	1.1370	0.9732	1.3282	1.05E-01
	Exonic	0.9371	0.8154	1.0761	3.58E-01	1.0951	0.8558	1.4027	4.71E-01	1.1561	0.9421	1.4182	1.64E-01	1.1660	0.9932	1.3691	6.05E-02
	Intronic	1.5676	0.9374	2.6645	9.00E-02	1.8301	0.8607	4.1014	1.26E-01	0.7676	0.3976	1.4456	4.19E-01	0.7474	0.3688	1.4535	4.00E-01
	Intergenic	1.1201	0.9522	1.3181	1.71E-01	1.2167	0.9451	1.5708	1.30E-01	0.8856	0.6938	1.1266	3.25E-01	0.8033	0.6700	0.9608	1.72E-02
Short (<100kb)	All	1.0490	0.9659	1.1394	2.56E-01	0.9958	0.9315	1.0646	9.03E-01	1.0871	1.0056	1.1754	3.57E-02	1.0692	1.0130	1.1316	1.83E-02
	Genic	1.1496	1.0281	1.2859	1.46E-02	0.9352	0.8489	1.0289	1.71E-01	1.0646	0.9517	1.1909	2.74E-01	1.0444	0.9716	1.1289	2.52E-01
	Exonic	1.2494	1.0913	1.4317	1.30E-03	0.9253	0.8209	1.0408	1.99E-01	1.1099	0.9632	1.2794	1.50E-01	1.0402	0.9524	1.1442	3.91E-01
	Intronic	0.9606	0.7893	1.1685	6.88E-01	0.9461	0.7912	1.1308	5.42E-01	0.9934	0.8280	1.1904	9.43E-01	1.0655	0.9266	1.2248	3.73E-01
	Intergenic	0.9367	0.8262	1.0616	3.06E-01	1.0730	0.9663	1.1919	1.88E-01	1.1197	0.9996	1.2543	5.08E-02	1.1050	1.0201	1.1972	1.44E-02

B. Duplications

Type of Dups	Type of CNV	RADIANT (<1%)				GenRED II (<1%)				GenRED (<1%)				NESDA/NTR (<1%)			
		OR	2.50%	97.50%	p value	OR	2.50%	97.50%	p value	OR	2.50%	97.50%	p value	OR	2.50%	97.50%	p value
Long (>100kb)	All	0.9371	0.8710	1.0079	8.12E-02	1.1422	1.0025	1.3028	4.65E-02	1.0229	0.8920	1.1721	7.45E-01	1.0790	1.0089	1.1602	3.22E-02
	Genic	0.8981	0.8267	0.9748	1.05E-02	1.1286	0.9731	1.3101	1.10E-01	1.0764	0.9284	1.2473	3.28E-01	1.0782	1.0054	1.1631	4.19E-02
	Exonic	0.8964	0.8248	0.9733	9.54E-03	1.1139	0.9598	1.2937	1.56E-01	1.0810	0.9318	1.2534	3.03E-01	1.0757	1.0031	1.1603	4.81E-02
	Intronic	1.1570	0.4079	3.3611	7.82E-01	8.2454	1.2159	163.4242	6.17E-02	0.4937	0.0243	3.5696	5.40E-01	2.0466	0.6157	7.8386	2.55E-01
	Intergenic	1.1327	0.9452	1.3585	1.77E-01	1.2350	0.9138	1.6742	1.71E-01	0.7823	0.5530	1.0966	1.59E-01	1.1096	0.8598	1.4309	4.23E-01
Short (<100kb)	All	1.0024	0.9264	1.0843	9.53E-01	0.9128	0.8439	0.9837	1.93E-02	1.0876	0.9835	1.2025	1.01E-01	0.9919	0.9412	1.0437	7.54E-01
	Genic	0.9793	0.8916	1.0749	6.60E-01	0.9915	0.8955	1.0967	8.69E-01	1.0420	0.9136	1.1879	5.39E-01	0.9745	0.9086	1.0420	4.56E-01
	Exonic	0.9503	0.8580	1.0513	3.25E-01	0.9707	0.8682	1.0833	5.97E-01	0.9800	0.8431	1.1381	7.92E-01	0.9931	0.9198	1.0704	8.57E-01
	Intronic	1.2247	0.9256	1.6247	1.57E-01	1.1558	0.8571	1.5628	3.44E-01	1.3057	0.9821	1.7377	6.65E-02	0.8053	0.6419	1.0042	5.74E-02
	Intergenic	1.0653	0.9163	1.2386	4.10E-01	0.7581	0.6574	0.8695	1.05E-04	1.1601	0.9902	1.3588	6.56E-02	1.0304	0.9246	1.1486	5.86E-01

Table S13. Logistic regression analyses of global burden of CNVs.

A. Deletions

Type of Del	Type of CNV	Tested effect	All (< 1%)				Singleton CNVs				> 500 kb CNVs				> 1 Mb CNVs			
			OR	2.50%	97.50%	p value	OR	2.50%	97.50%	p value	OR	2.50%	97.50%	p value	OR	2.50%	97.50%	p value
Long (> 100 kb or longer)	All	NSEG	1.0296	0.9658	1.0975	3.71E-01	1.1068	0.9466	1.2940	2.03E-01	1.1369	0.8832	1.4637	3.19E-01	1.4435	0.8839	2.3822	1.45E-01
		KB	1.0001	0.9999	1.0003	3.08E-01	1.0001	0.9996	1.0007	6.72E-01	1.0002	0.9999	1.0005	2.08E-01	1.0002	0.9999	1.0006	2.34E-01
	Gene-containing	NSEG	1.0606	0.9754	1.1531	1.68E-01	1.0987	0.9169	1.3164	3.07E-01	1.1239	0.8586	1.4707	3.94E-01	1.3108	0.7780	2.2253	3.10E-01
		KB	1.0001	0.9999	1.0004	2.35E-01	1.0002	0.9996	1.0007	5.29E-01	1.0001	0.9999	1.0004	3.20E-01	1.0002	0.9998	1.0005	3.98E-01
	Exon-containing	NSEG	1.0521	0.9646	1.1475	2.51E-01	1.1105	0.9242	1.3343	2.63E-01	1.1239	0.8586	1.4707	3.94E-01	1.3108	0.7780	2.2253	3.10E-01
		KB	1.0001	0.9999	1.0004	2.69E-01	1.0002	0.9997	1.0008	4.16E-01	1.0001	0.9999	1.0004	3.20E-01	1.0002	0.9998	1.0005	3.98E-01
	Intronic	NSEG	1.1672	0.8591	1.5876	3.23E-01	1.2429	0.6541	2.3868	5.07E-01	NA	NA	NA	NA	NA	NA	NA	NA
		KB	1.0008	0.9988	1.0028	4.49E-01	1.0002	0.9956	1.0048	9.32E-01	NA	NA	NA	NA	NA	NA	NA	NA
	Intergenic	NSEG	0.9881	0.8956	1.0899	8.11E-01	1.1758	0.9066	1.5248	2.22E-01	1.2482	0.5924	2.6818	5.61E-01	3.1975	0.7163	22.2489	1.62E-01
		KB	1.0000	0.9995	1.0004	9.20E-01	1.0005	0.9992	1.0019	4.67E-01	1.0005	0.9996	1.0015	3.04E-01	1.0009	0.9996	1.0025	1.98E-01
Short (< 100 kb)	All	NSEG	1.0483	1.0139	1.0843	5.92E-03	1.0664	0.9955	1.1473	7.70E-02								
		KB	1.0011	1.0004	1.0019	3.93E-03	1.0020	1.0003	1.0037	2.32E-02								
	Gene-containing	NSEG	1.0343	0.9877	1.0842	1.56E-01	1.0224	0.9377	1.1191	6.17E-01								
		KB	1.0010	1.0000	1.0021	4.74E-02	1.0012	0.9993	1.0033	2.41E-01								
	Exon-containing	NSEG	1.0552	0.9965	1.1192	6.95E-02	1.0360	0.9382	1.1510	4.90E-01								
		KB	1.0013	1.0002	1.0025	2.61E-02	1.0013	0.9992	1.0035	2.52E-01								
	Intronic	NSEG	0.9952	0.9149	1.0825	9.11E-01	0.9425	0.7822	1.1342	5.31E-01								
		KB	1.0001	0.9979	1.0022	9.39E-01	0.9998	0.9948	1.0049	9.46E-01								
	Intergenic	NSEG	1.0716	1.0190	1.1270	7.14E-03	1.1574	1.0338	1.2962	1.13E-02								
		KB	1.0014	1.0002	1.0026	2.26E-02	1.0032	1.0006	1.0059	1.74E-02								

(continues on next page)

B. Duplications

Type of Dup	Type of CNV	Tested effect	All (< 1%)				Singleton CNVs				> 500 kb CNVs				> 1 Mb CNVs			
			OR	2.50%	97.50%	p value	OR	2.50%	97.50%	p value	OR	2.50%	97.50%	p value	OR	2.50%	97.50%	p value
Long (> 100 kb or longer)	All	NSEG	1.0268	0.9837	1.0725	2.29E-01	1.1097	0.9876	1.2484	8.13E-02	0.9819	0.8599	1.1207	7.87E-01	0.9906	0.7461	1.3136	9.48E-01
		KB	1.0000	0.9999	1.0001	5.29E-01	1.0002	0.9998	1.0006	3.26E-01	1.0000	0.9999	1.0001	9.32E-01	1.0000	0.9999	1.0002	7.75E-01
	Gene-containing	NSEG	1.0187	0.9723	1.0677	4.37E-01	1.0483	0.9236	1.1908	4.66E-01	0.9708	0.8438	1.1165	6.79E-01	0.9466	0.7075	1.2643	7.11E-01
		KB	1.0000	0.9999	1.0001	8.93E-01	1.0000	0.9996	1.0004	9.63E-01	1.0000	0.9998	1.0001	7.10E-01	1.0000	0.9998	1.0001	7.54E-01
	Exon-containing	NSEG	1.0166	0.9702	1.0657	4.89E-01	1.0426	0.9179	1.1850	5.21E-01	0.9708	0.8438	1.1165	6.79E-01	0.9466	0.7075	1.2643	7.11E-01
		KB	1.0000	0.9999	1.0001	9.10E-01	1.0000	0.9996	1.0003	8.54E-01	1.0000	0.9998	1.0001	7.10E-01	1.0000	0.9998	1.0001	7.54E-01
	Intronic	NSEG	1.5254	0.7880	3.0095	2.13E-01	1.3693	0.5310	3.6480	5.16E-01	NA	NA	NA	NA	NA	NA	NA	NA
		KB	1.0007	0.9981	1.0033	6.11E-01	1.0026	0.9956	1.0100	4.79E-01	NA	NA	NA	NA	NA	NA	NA	NA
	Intergenic	NSEG	1.0912	0.9654	1.2333	1.62E-01	1.1908	0.9304	1.5262	1.66E-01	1.0894	0.7098	1.6726	6.94E-01	2.4597	0.6690	11.6064	1.99E-01
		KB	1.0002	0.9999	1.0005	1.55E-01	1.0006	0.9995	1.0016	3.04E-01	1.0002	0.9999	1.0006	2.34E-01	1.0004	0.9999	1.0010	1.49E-01
Short (< 100 kb)	All	NSEG	0.9850	0.9512	1.0194	3.90E-01	0.9925	0.9219	1.0681	8.41E-01								
		KB	0.9997	0.9990	1.0004	4.69E-01	1.0000	0.9986	1.0015	9.45E-01								
	Gene-containing	NSEG	0.9845	0.9410	1.0296	4.96E-01	0.9607	0.8716	1.0581	4.17E-01								
		KB	0.9999	0.9990	1.0007	7.73E-01	0.9998	0.9981	1.0015	8.15E-01								
	Exon-containing	NSEG	0.9730	0.9253	1.0225	2.83E-01	0.9392	0.8452	1.0426	2.41E-01								
		KB	0.9997	0.9989	1.0006	5.72E-01	0.9995	0.9977	1.0013	5.78E-01								
	Intronic	NSEG	1.0586	0.9285	1.2066	3.94E-01	0.9088	0.7050	1.1681	4.57E-01								
		KB	1.0017	0.9983	1.0051	3.18E-01	0.9983	0.9924	1.0042	5.75E-01								
	Intergenic	NSEG	0.9788	0.9166	1.0449	5.21E-01	1.0510	0.9282	1.1911	4.33E-01								
		KB	0.9993	0.9978	1.0007	3.17E-01	1.0009	0.9983	1.0035	4.87E-01								

Shown are results of logistic regression analysis for all kinds of deletions and duplications using batch and sex as covariates.

Table S14. Meta-analysis of global CNV burden.

A. Deletions

Type of Deletion	Type of CNV	RADIANT All (<1%)		GR Illum All (<1%)		GR Affy All (<1%)		Neth All (<1%)		Cochran's Q-test p-value	Fixed effect model			
		Beta	SE	Beta	SE	Beta	SE	Beta	SE		Beta	2.50%	97.50%	p-value
Long (>100kb)	All	0.0283	0.0531	0.1723	0.0896	0.0166	0.0778	-0.0213	0.0593	0.3475	0.0303	-0.0340	0.0947	0.3551
	Genic	-0.0306	0.0688	0.1385	0.1188	0.1071	0.0996	0.1284	0.0793	0.3719	0.0638	-0.0204	0.1480	0.1376
	Exonic	-0.0650	0.0707	0.0909	0.1259	0.1450	0.1043	0.1536	0.0818	0.1607	0.0575	-0.0297	0.1448	0.1964
	Intronic	0.4495	0.2652	0.6044	0.3945	-0.2645	0.3271	-0.2912	0.3458	0.1201	0.1399	-0.1765	0.4564	0.3861
	Intergenic	0.1134	0.0829	0.1961	0.1294	-0.1215	0.1235	-0.2190	0.0919	0.0133	-0.0146	-0.1140	0.0847	0.7732
Short (<100kb)	All	0.0479	0.0421	-0.0042	0.0340	0.0835	0.0398	0.0669	0.0284	0.3086	0.0482	0.0141	0.0823	0.0056
	Genic	0.1394	0.0571	-0.0670	0.0489	0.0626	0.0572	0.0434	0.0379	0.0467	0.0371	-0.0101	0.0843	0.1230
	Exonic	0.2226	0.0692	-0.0777	0.0604	0.1043	0.0724	0.0394	0.0459	0.0103	0.0555	-0.0023	0.1134	0.0598
	Intronic	-0.0402	0.1000	-0.0554	0.0910	-0.0066	0.0925	0.0634	0.0711	0.7219	0.0020	-0.0827	0.0867	0.9635
	Intergenic	-0.0654	0.0639	0.0705	0.0535	0.1130	0.0579	0.0999	0.0408	0.1342	0.0685	0.0178	0.1192	0.0081

B. Duplications

Type of Duplication	Type of CNV	RADIANT All (<1%)		GR Illum All (<1%)		GR Affy All (<1%)		Neth All (<1%)		Cochran's Q-test p-value	Fixed effect model			
		Beta	SE	Beta	SE	Beta	SE	Beta	SE		Beta	2.50%	97.50%	p-value
Long (>100kb)	All	-0.0649	0.0372	0.1329	0.0668	0.0227	0.0696	0.0760	0.0355	0.0147	0.0246	-0.0198	0.0690	0.2779
	Genic	-0.1075	0.0420	0.1210	0.0758	0.0736	0.0753	0.0753	0.0370	0.0033	0.0171	-0.0312	0.0653	0.4887
	Exonic	-0.1094	0.0422	0.1079	0.0761	0.0779	0.0756	0.0730	0.0369	0.0040	0.0149	-0.0335	0.0632	0.5466
	Intronic	0.1458	0.5274	2.1097	1.1290	-0.7059	1.1516	0.7162	0.6287	0.2981	0.4513	-0.2566	1.1593	0.2115
	Intergenic	0.1246	0.0924	0.2111	0.1541	-0.2456	0.1743	0.1040	0.1298	0.2148	0.0858	-0.0378	0.2094	0.1737
Short (<100kb)	All	0.0024	0.0401	-0.0913	0.0390	0.0839	0.0512	-0.0082	0.0261	0.0505	-0.0123	-0.0474	0.0227	0.4905
	Genic	-0.0209	0.0476	-0.0085	0.0516	0.0411	0.0669	-0.0258	0.0346	0.8433	-0.0132	-0.0585	0.0320	0.5671
	Exonic	-0.0510	0.0517	-0.0298	0.0564	-0.0202	0.0765	-0.0069	0.0383	0.9222	-0.0238	-0.0737	0.0262	0.3511
	Intronic	0.2027	0.1433	0.1448	0.1529	0.2667	0.1454	-0.2165	0.1139	0.0266	0.0556	-0.0778	0.1890	0.4144
	Intergenic	0.0633	0.0768	-0.2770	0.0714	0.1485	0.0807	0.0300	0.0551	0.0002	-0.0129	-0.0801	0.0544	0.7078

Shown are results of global burden meta-analysis. Beta and SE are coefficient and its standard error from logistic regression.

Table S15. Logistic regression analyses of global burden of short deletions with various sizes.

Deletion size	CNVs/subject		OR	95% CI	Effect size	p value
	Cases	Control				
10-20 kb	0.3379	0.3298	1.0447	0.9840-1.1093	0.0438	1.52E-01
20-30 kb	0.1708	0.1702	1.0313	0.9468-1.1233	0.0308	4.80E-01
30-40 kb	0.1265	0.1186	1.0886	0.9825-1.2062	0.0849	1.05E-01
40-50 kb	0.0998	0.1031	0.9843	0.8793-1.1016	-0.0158	7.84E-01
50-60 kb	0.0644	0.0663	0.9675	0.8442-1.1077	-0.0331	6.32E-01
60-70 kb	0.0673	0.0552	1.2465	1.0794-1.4403	0.2204	**2.73E-03**
70-80 kb	0.0581	0.0521	1.1204	0.9630-1.3041	0.1137	1.41E-01
80-90 kb	0.0505	0.0391	1.2945	1.0933-1.5340	0.2581	**2.80E-03**
90-100 kb	0.0396	0.0433	0.9134	0.7661-1.0877	-0.0906	3.11E-01

Table S16. Logistic regression analyses of global burden of all rare deletions and duplications.

Type of CNV	Type of CNV	Combined cohort			
		OR	2.50%	97.50%	p value
All rare deletion	All	1.0435	1.0134	1.0748	4.56E-03
	Gene-containing	1.0402	0.9990	1.0837	5.77E-02
	Exon-containing	1.0537	1.0048	1.1060	3.25E-02
	Intronic	1.0064	0.9280	1.0913	8.77E-01
	Intergenic	1.0530	1.0071	1.1010	2.30E-02
All rare duplication	All	1.0010	0.9764	1.0261	9.39E-01
	Gene-containing	1.0007	0.9715	1.0306	9.65E-01
	Exon-containing	0.9966	0.9661	1.0279	8.31E-01
	Intronic	1.0730	0.9438	1.2195	2.81E-01
	Intergenic	1.0026	0.9473	1.0610	9.28E-01

Table S17. Global burden analyses of rare CNVs after filtering common CNVs within each cohort separately rather than in all cohorts.

A. Deletions

Type of Del	Type of CNV	Tested effect	All (<1%)			Singleton CNVs			> 500 kb CNVs			> 1 Mb CNVs		
			Cases	Controls	p value	Cases	Controls	p value	Cases	Controls	p value	Cases	Controls	p value
Long (> 100 kb or longer)	All	CNVs/subj	0.3336	0.3266	1.76E-01	0.0559	0.0501	8.11E-02	0.0216	0.0189	2.06E-01	0.0066	0.0044	9.50E-02
		Subjs w CNV	0.2879	0.2774	5.66E-02	0.0547	0.0485	6.50E-02	0.0215	0.0186	1.91E-01	0.0066	0.0044	9.50E-02
	Intergenic	CNVs/subj	0.1370	0.1402	6.12E-01	0.0206	0.0180	1.07E-01	0.0028	0.0020	3.94E-01	0.0010	0.0003	1.18E-01
		Subjs w CNV	0.1275	0.1319	6.98E-01	0.0204	0.0178	1.14E-01	0.0028	0.0020	3.94E-01	0.0010	0.0003	1.18E-01
	Gene-containing	CNVs/subj	0.1965	0.1864	7.46E-02	0.0420	0.0377	1.49E-01	0.0189	0.0169	2.37E-01	0.0055	0.0041	2.03E-01
		Subjs w CNV	0.1820	0.1678	1.34E-02	0.0412	0.0371	1.66E-01	0.0189	0.0166	1.99E-01	0.0055	0.0041	2.03E-01
		Genes/CNV	0.7367	0.7247	3.74E-01	0.1285	0.1422	8.00E-01	0.2097	0.1656	1.09E-01	0.0931	0.0457	4.63E-02
		Genes/CNV kb	0.0099	0.0099	5.57E-01	0.0120	0.0132	8.91E-01	0.0113	0.0116	3.73E-01	0.0100	0.0079	1.66E-01
	Exon-containing	CNVs/subj	0.1815	0.1742	1.07E-01	0.0410	0.0365	1.24E-01	0.0189	0.0169	2.39E-01	0.0055	0.0041	2.00E-01
		Subjs w CNV	0.1682	0.1582	3.60E-02	0.0403	0.0359	1.29E-01	0.0189	0.0166	2.01E-01	0.0055	0.0041	2.00E-01
		Genes/CNV	3.9980	3.8080	2.69E-01	0.6933	0.7514	7.29E-01	1.3940	1.0450	6.51E-02	0.6121	0.3052	5.52E-02
		Genes/CNV kb	0.0484	0.0479	5.01E-01	0.0588	0.0676	9.20E-01	0.0742	0.0727	2.55E-01	0.0639	0.0525	2.03E-01
	Intronic	CNVs/subj	0.0151	0.0122	2.07E-01	0.0036	0.0027	3.54E-01	0.0000	0.0000	1.00E+00	0.0000	0.0000	1.00E+00
		Subjs w CNV	0.0151	0.0119	1.70E-01	0.0036	0.0027	3.54E-01	0.0000	0.0000	1.00E+00	0.0000	0.0000	1.00E+00
Short (< 100 kb)	All	CNVs/subj	1.0760	1.0200	2.10E-04	0.2154	0.2021	4.90E-02						
		Subjs w CNV	0.6040	0.5909	2.54E-03	0.1869	0.1730	8.46E-03						
	Intergenic	CNVs/subj	0.5564	0.5155	1.60E-04	0.1047	0.0928	1.10E-02						
		Subjs w CNV	0.3986	0.3838	5.40E-03	0.0972	0.0872	1.43E-02						
	Gene-containing	CNVs/subj	0.5197	0.5045	4.96E-02	0.1178	0.1162	3.34E-01						
		Subjs w CNV	0.3844	0.3741	2.30E-02	0.1061	0.1055	3.47E-01						
		Genes/CNV	0.9059	0.8676	4.28E-02	0.2087	0.1960	2.16E-01						
		Genes/CNV kb	0.0264	0.0277	8.22E-01	0.0323	0.0344	7.69E-01						
	Exon-containing	CNVs/subj	0.3349	0.3151	2.97E-02	0.0895	0.0859	2.85E-01						
		Subjs w CNV	0.2727	0.2563	6.81E-03	0.0810	0.0788	3.40E-01						
		Genes/CNV	2.1480	1.9660	5.34E-02	0.5413	0.5088	3.75E-01						
		Genes/CNV kb	0.0523	0.0513	4.51E-01	0.0667	0.0683	7.92E-01						
	Intronic	CNVs/subj	0.1848	0.1894	4.17E-01	0.0351	0.0388	7.27E-01						
		Subjs w CNV	0.1666	0.1677	2.54E-01	0.0337	0.0377	7.47E-01						

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B. Duplications

Type of Dup	Type of CNV	Tested effect	All (< 1%)			Singleton CNVs			> 500 kb CNVs			> 1 Mb CNVs		
			Cases	Controls	p value	Cases	Controls	p value	Cases	Controls	p value	Cases	Controls	p value
Long (> 100 kb or longer)	All	CNVs/subj	0.5298	0.5072	8.29E-02	0.0862	0.0746	2.52E-02	0.0735	0.0727	6.10E-01	0.0173	0.0166	5.14E-01
		Subjs w CNV	0.3879	0.3824	3.55E-01	0.0777	0.0693	4.70E-02	0.0694	0.0697	6.92E-01	0.0170	0.0163	5.14E-01
	Intergenic	CNVs/subj	0.0886	0.0818	1.18E-01	0.0225	0.0186	7.92E-02	0.0076	0.0066	4.12E-01	0.0012	0.0005	1.73E-01
		Subjs w CNV	0.0837	0.0771	1.19E-01	0.0218	0.0181	8.31E-02	0.0076	0.0066	4.12E-01	0.0012	0.0005	1.73E-01
	Gene-containing	CNVs/subj	0.4412	0.4254	1.46E-01	0.0702	0.0644	1.79E-01	0.0659	0.0661	6.59E-01	0.0161	0.0162	6.28E-01
		Subjs w CNV	0.3362	0.3319	3.65E-01	0.0633	0.0608	3.63E-01	0.0630	0.0635	6.79E-01	0.0157	0.0159	6.30E-01
		Genes/CNV	2.6420	2.6400	4.79E-01	0.2903	0.2703	3.95E-01	0.8031	0.8648	7.51E-01	0.3465	0.3842	7.08E-01
		Genes/CNV kb	0.0171	0.0181	9.68E-01	0.0162	0.0172	8.43E-01	0.0122	0.0130	6.54E-01	0.0126	0.0133	5.62E-01
	Exon-containing	CNVs/subj	0.4375	0.4230	1.69E-01	0.0694	0.0641	2.06E-01	0.0659	0.0661	6.59E-01	0.0161	0.0162	6.26E-01
		Subjs w CNV	0.3336	0.3308	4.40E-01	0.0628	0.0605	3.76E-01	0.0630	0.0635	6.80E-01	0.0157	0.0159	6.27E-01
		Genes/CNV	15.9500	15.6200	3.68E-01	1.6970	1.6030	4.82E-01	5.5020	5.9640	7.53E-01	2.4240	2.7310	7.18E-01
		Genes/CNV kb	0.0933	0.0946	6.86E-01	0.0894	0.0960	8.84E-01	0.0837	0.0877	5.63E-01	0.0879	0.0953	5.98E-01
	Intronic	CNVs/subj	0.0036	0.0024	1.03E-01	0.0017	0.0012	2.88E-01	0.0000	0.0000	1.00E+00	0.0000	0.0000	1.00E+00
		Subjs w CNV	0.0036	0.0024	1.03E-01	0.0017	0.0012	2.88E-01	0.0000	0.0000	1.00E+00	0.0000	0.0000	1.00E+00
Short (< 100 kb)	All	CNVs/subj	0.7299	0.7588	7.09E-01	0.1709	0.1778	6.68E-01						
		Subjs w CNV	0.4917	0.4881	1.21E-01	0.1514	0.1476	1.49E-01						
	Intergenic	CNVs/subj	0.2855	0.2932	4.78E-01	0.0706	0.0699	2.52E-01						
		Subjs w CNV	0.2412	0.2410	1.85E-01	0.0677	0.0631	5.87E-02						
	Gene-containing	CNVs/subj	0.4445	0.4656	7.81E-01	0.1064	0.1136	8.55E-01						
		Subjs w CNV	0.3407	0.3390	2.49E-01	0.0962	0.0981	5.94E-01						
		Genes/CNV	0.9993	1.0670	8.87E-01	0.2272	0.2377	7.12E-01						
		Genes/CNV kb	0.0328	0.0327	6.16E-01	0.0325	0.0337	7.44E-01						
	Exon-containing	CNVs/subj	0.3664	0.3873	8.40E-01	0.0895	0.0977	9.12E-01						
		Subjs w CNV	0.2901	0.2911	4.12E-01	0.0813	0.0848	7.56E-01						
		Genes/CNV	3.7000	3.8390	7.45E-01	0.7990	0.8521	7.72E-01						
		Genes/CNV kb	0.1045	0.0996	2.71E-01	0.0939	0.1026	9.06E-01						
	Intronic	CNVs/subj	0.0780	0.0783	3.76E-01	0.0190	0.0220	8.33E-01						
		Subjs w CNV	0.0746	0.0731	2.28E-01	0.0189	0.0217	8.30E-01						

Shown are results of whole genome burden analyses on combined data of CNV calls after filtering common CNVs within each cohort separately.

Table S18. Global burden analyses of CNVs called by both QuantiSNP and PennCNV for Illumina data and by Birdsuite for Affymetrix data.

A. Deletions

Type of Del	Type of CNV	Tested effect	All (<1%)			Singleton CNVs			> 500 kb CNVs			> 1 Mb CNVs		
			Cases	Controls	p value	Cases	Controls	p value	Cases	Controls	p value	Cases	Controls	p value
Long (> 100 kb or longer)	All	CNVs/subj	0.3163	0.3100	1.51E-01	0.0547	0.0486	6.35E-02	0.0215	0.0187	2.08E-01	0.0064	0.0044	1.11E-01
		Subjs w CNV	0.2756	0.2658	5.25E-02	0.0535	0.0469	4.93E-02	0.0213	0.0184	1.92E-01	0.0064	0.0044	1.11E-01
	Intergenic	CNVs/subj	0.1301	0.1357	7.08E-01	0.0202	0.0178	1.11E-01	0.0026	0.0020	4.50E-01	0.0009	0.0003	1.72E-01
		Subjs w CNV	0.1215	0.1283	7.98E-01	0.0201	0.0177	1.18E-01	0.0026	0.0020	4.50E-01	0.0009	0.0003	1.72E-01
	Gene-containing	CNVs/subj	0.1862	0.1743	3.66E-02	0.0412	0.0362	1.05E-01	0.0189	0.0168	2.24E-01	0.0055	0.0041	2.00E-01
		Subjs w CNV	0.1732	0.1586	8.14E-03	0.0403	0.0356	1.16E-01	0.0189	0.0165	1.87E-01	0.0055	0.0041	2.00E-01
		Genes/CNV	0.6995	0.6357	6.71E-02	0.1270	0.1361	7.23E-01	0.2097	0.1567	7.26E-02	0.0931	0.0457	4.66E-02
		Genes/CNV kb	0.0098	0.0093	1.78E-01	0.0120	0.0127	8.14E-01	0.0114	0.0110	2.68E-01	0.0103	0.0079	1.46E-01
	Exon-containing	CNVs/subj	0.1711	0.1621	5.35E-02	0.0401	0.0350	8.32E-02	0.0189	0.0168	2.23E-01	0.0055	0.0041	2.00E-01
		Subjs w CNV	0.1593	0.1488	2.30E-02	0.0395	0.0344	8.59E-02	0.0189	0.0165	1.87E-01	0.0055	0.0041	2.00E-01
		Genes/CNV	3.7430	3.2060	3.38E-02	0.6834	0.7126	6.38E-01	1.3940	0.9834	4.00E-02	0.6121	0.3052	5.57E-02
		Genes/CNV kb	0.0465	0.0427	1.18E-01	0.0581	0.0637	8.39E-01	0.0748	0.0685	1.68E-01	0.0657	0.0525	1.83E-01
	Intronic	CNVs/subj	0.0151	0.0122	2.07E-01	0.0036	0.0027	3.56E-01	0.0000	0.0000	1.00E+00	0.0000	0.0000	1.00E+00
		Subjs w CNV	0.0151	0.0119	1.71E-01	0.0036	0.0027	3.56E-01	0.0000	0.0000	1.00E+00	0.0000	0.0000	1.00E+00
Short (< 100 kb)	All	CNVs/subj	0.9524	0.9042	6.00E-05	0.2099	0.1890	2.51E-03						
		Subjs w CNV	0.5645	0.5572	5.98E-03	0.1811	0.1637	7.00E-04						
	Intergenic	CNVs/subj	0.4789	0.4491	2.60E-04	0.1022	0.0884	2.22E-03						
		Subjs w CNV	0.3578	0.3471	6.17E-03	0.0952	0.0835	3.16E-03						
	Gene-containing	CNVs/subj	0.4735	0.4550	1.09E-02	0.1145	0.1067	6.58E-02						
		Subjs w CNV	0.3621	0.3518	9.79E-03	0.1031	0.0987	8.18E-02						
		Genes/CNV	0.8320	0.7822	7.28E-03	0.2066	0.1778	2.16E-02						
		Genes/CNV kb	0.0276	0.0279	4.82E-01	0.0326	0.0334	4.62E-01						
	Exon-containing	CNVs/subj	0.3042	0.2818	5.26E-03	0.0869	0.0768	3.41E-02						
		Subjs w CNV	0.2542	0.2386	4.65E-03	0.0787	0.0720	5.05E-02						
		Genes/CNV	1.9670	1.7550	1.21E-02	0.5441	0.4555	8.59E-02						
		Genes/CNV kb	0.0542	0.0515	2.38E-01	0.0661	0.0635	5.05E-01						
	Intronic	CNVs/subj	0.1694	0.1733	3.46E-01	0.0337	0.0367	6.02E-01						
		Subjs w CNV	0.1547	0.1559	2.16E-01	0.0324	0.0358	6.41E-01						

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B. Duplications

Type of Dup	Type of CNV	Tested effect	All (< 1%)			Singleton CNVs			> 500 kb CNVs			> 1 Mb CNVs		
			Cases	Controls	p value	Cases	Controls	p value	Cases	Controls	p value	Cases	Controls	p value
Long (> 100 kb or longer)	All	CNVs/subj	0.4282	0.4147	1.19E-01	0.0766	0.0702	1.36E-01	0.0671	0.0644	4.11E-01	0.0145	0.0142	5.86E-01
		Subjs w CNV	0.3334	0.3293	3.17E-01	0.0699	0.0667	3.08E-01	0.0638	0.0628	5.48E-01	0.0144	0.0142	6.11E-01
	Intergenic	CNVs/subj	0.0671	0.0697	6.82E-01	0.0182	0.0168	3.54E-01	0.0061	0.0060	6.21E-01	0.0005	0.0003	4.81E-01
		Subjs w CNV	0.0652	0.0670	6.54E-01	0.0182	0.0163	2.71E-01	0.0061	0.0060	6.21E-01	0.0005	0.0003	4.81E-01
	Gene-containing	CNVs/subj	0.3611	0.3450	7.56E-02	0.0649	0.0599	1.96E-01	0.0611	0.0584	3.84E-01	0.0140	0.0139	6.17E-01
		Subjs w CNV	0.2891	0.2819	1.76E-01	0.0587	0.0575	4.84E-01	0.0588	0.0571	4.53E-01	0.0138	0.0139	6.42E-01
		Genes/CNV	2.1920	2.0200	9.28E-02	0.2645	0.2483	3.81E-01	0.7280	0.6980	3.51E-01	0.3062	0.3346	6.66E-01
		Genes/CNV kb	0.0173	0.0168	2.71E-01	0.0161	0.0161	5.42E-01	0.0121	0.0114	1.57E-01	0.0133	0.0133	3.76E-01
	Exon-containing	CNVs/subj	0.3576	0.3426	8.82E-02	0.0640	0.0596	2.25E-01	0.0611	0.0584	3.85E-01	0.0140	0.0139	6.18E-01
		Subjs w CNV	0.2867	0.2809	2.26E-01	0.0581	0.0572	4.96E-01	0.0588	0.0571	4.55E-01	0.0138	0.0139	6.44E-01
		Genes/CNV	13.3900	12.0900	6.38E-02	1.5240	1.4700	4.61E-01	5.0550	4.8670	3.38E-01	2.1960	2.4320	6.63E-01
		Genes/CNV kb	0.0936	0.0871	1.98E-02	0.0859	0.0884	6.97E-01	0.0843	0.0777	7.59E-02	0.0953	0.0976	4.07E-01
	Intronic	CNVs/subj	0.0035	0.0024	1.25E-01	0.0016	0.0012	3.58E-01	0.0000	0.0000	1.00E+00	0.0000	0.0000	1.00E+00
		Subjs w CNV	0.0035	0.0024	1.25E-01	0.0016	0.0012	3.58E-01	0.0000	0.0000	1.00E+00	0.0000	0.0000	1.00E+00
Short (< 100 kb)	All	CNVs/subj	0.5389	0.5542	3.91E-01	0.1464	0.1542	6.19E-01						
		Subjs w CNV	0.3952	0.3957	1.47E-01	0.1318	0.1310	1.61E-01						
	Intergenic	CNVs/subj	0.2093	0.2129	2.75E-01	0.0614	0.0623	3.40E-01						
		Subjs w CNV	0.1849	0.1832	1.04E-01	0.0597	0.0571	9.88E-02						
	Gene-containing	CNVs/subj	0.3296	0.3412	5.24E-01	0.0903	0.0966	7.39E-01						
		Subjs w CNV	0.2675	0.2695	2.93E-01	0.0824	0.0854	5.59E-01						
		Genes/CNV	0.7211	0.7701	8.13E-01	0.1919	0.2006	6.05E-01						
		Genes/CNV kb	0.0316	0.0334	9.57E-01	0.0304	0.0331	8.92E-01						
	Exon-containing	CNVs/subj	0.2689	0.2781	5.58E-01	0.0773	0.0810	6.42E-01						
		Subjs w CNV	0.2244	0.2274	4.20E-01	0.0706	0.0723	5.06E-01						
		Genes/CNV	2.7030	2.6270	2.47E-01	0.6865	0.6951	5.56E-01						
		Genes/CNV kb	0.0999	0.0966	4.29E-01	0.0908	0.0951	8.16E-01						
	Intronic	CNVs/subj	0.0607	0.0631	4.38E-01	0.0152	0.0204	9.61E-01						
		Subjs w CNV	0.0581	0.0590	3.08E-01	0.0151	0.0201	9.61E-01						

Shown are results of whole genome burden analyses on combined data of only CNV calls reported by both QuantiSNP and PennCNV from Illumina data and Birdsuite calls from Affymetrix data.

Table S19. Global burden analyses of CNVs after excluding nominally significant CNV regions that failed manual checks.

CNV type	CNVs/subject		OR	95% CI	p value
	Cases	Cont			
Deletions					
>100kb — All	0.324	0.318	1.0296	0.9658-1.0975	3.71E-01
Intergenic	0.134	0.138	0.9881	0.8956-1.0899	8.11E-01
Genic	0.191	0.181	1.0606	0.9754-1.1531	1.68E-01
Exonic	0.175	0.168	1.0521	0.9646-1.1475	2.51E-01
Intronic	0.015	0.012	1.1672	0.8591-1.5876	3.23E-01
<100kb — All	1.014	0.977	1.0481	1.0137-1.0841	***6.13E-03***
Intergenic	0.506	0.483	1.0711	1.0185-1.1265	*7.51E-03*
Genic	0.508	0.494	1.0343	0.9877-1.0842	1.56E-01
Exonic	0.329	0.310	1.0539	0.9953-1.1178	7.61E-02
Intronic	0.178	0.184	0.9978	0.9172-1.0855	9.60E-01
Duplications					
>100kb — All	0.496	0.476	1.0262	0.9830-1.0718	2.40E-01
Intergenic	0.087	0.079	1.0912	0.9654-1.2333	1.62E-01
Genic	0.409	0.397	1.0179	0.9716-1.0669	4.56E-01
Exonic	0.405	0.395	1.0159	0.9695-1.0649	5.10E-01
Intronic	0.004	0.002	1.5254	0.7880-3.0095	2.13E-01
<100kb — All	0.668	0.701	0.9831	0.9493-1.0175	3.33E-01
Intergenic	0.250	0.265	0.9736	0.9116-1.0395	4.23E-01
Genic	0.417	0.436	0.9838	0.9402-1.0288	4.76E-01
Exonic	0.344	0.364	0.9729	0.9251-1.0224	2.80E-01
Intronic	0.073	0.072	1.0532	0.9237-1.2006	4.38E-01

Table S20. DNA sample sources of the subjects included in this dataset.

Cohort	# Cases	# Controls	Total	Source
RADIANT	2,460	2,587	5,047	Blood
NESDA/NTR	1,568	1,913	3,481	Blood
GenRED II	811	862	1,673	Blood (137 cases & 862 controls); LCL (674 cases)
GenRED	941	1,264	2,205	Blood (7 controls); LCL (941 cases & 1257 controls)

Table S21. CNV burden comparison between blood vs. LCL case DNAs in cohort GenRED II.

Type of CNV	Type of CNV	CNVs/subject		Permutation p-value	Logistic Regression			
		Blood	LCL		OR	2.50%	97.50%	p value
Long deletion (>100kb)	All	0.2920	0.3991	0.9815	0.7078	0.4923	0.9908	5.21E-02
	Genic	0.1679	0.2211	0.9243	0.7343	0.4513	1.1443	1.91E-01
	Exonic	0.1606	0.1929	0.8290	0.8158	0.4948	1.2868	4.01E-01
	Intronic	0.0073	0.0282	0.9768	0.2527	0.0140	1.2340	1.82E-01
	Intergenic	0.1241	0.1780	0.9401	0.6943	0.4011	1.1241	1.63E-01
Short deletion (<100kb)	All	1.6060	1.7200	0.8107	0.9439	0.8237	1.0747	3.94E-01
	Genic	0.7883	0.8442	0.7501	0.9373	0.7633	1.1394	5.25E-01
	Exonic	0.4818	0.5549	0.8678	0.8710	0.6657	1.1193	2.96E-01
	Intronic	0.3066	0.2893	0.3909	1.0616	0.7467	1.4735	7.29E-01
	Intergenic	0.8175	0.8754	0.7488	0.9407	0.7720	1.1331	5.31E-01
Long duplication (>100kb)	All	0.5839	0.5623	0.4026	1.0348	0.8164	1.2943	7.71E-01
	Genic	0.4745	0.4451	0.3477	1.0594	0.8138	1.3579	6.58E-01
	Exonic	0.4599	0.4407	0.4075	1.0389	0.7956	1.3345	7.72E-01
	Intronic	0.0146	0.0045	0.1994	3.3495	0.4369	20.4738	1.89E-01
	Intergenic	0.1095	0.1172	0.6413	0.9321	0.5123	1.5852	8.06E-01
Short duplication (<100kb)	All	1.1610	1.0820	0.2409	1.0589	0.9042	1.2298	4.64E-01
	Genic	0.8029	0.6988	0.1121	1.1387	0.9277	1.3859	2.03E-01
	Exonic	0.6861	0.5816	0.0919	1.1696	0.9348	1.4501	1.60E-01
	Intronic	0.1168	0.1172	0.5465	0.9964	0.5647	1.6434	9.89E-01
	Intergenic	0.3577	0.3828	0.6667	0.9472	0.7081	1.2311	6.99E-01

Table S22. Logistic regression analyses of global burden of CNVs for RADIANT cases vs. screened controls and for RADIANT cases vs. unscreened NBS samples.

Type of Deletion	Type of CNV	RADIANT cases vs screened controls				RADIANT cases vs unscreened NBS controls			
		OR	2.50%	97.50%	p value	OR	2.50%	97.50%	p value
Long (>100kb)	All	1.0562	0.8677	1.2989	5.95E-01	1.0237	0.9185	1.1412	6.72E-01
	Gene-containing	1.1273	0.8654	1.4975	3.91E-01	0.9480	0.8241	1.0903	4.54E-01
	Exon-containing	1.1201	0.8527	1.5036	4.32E-01	0.9115	0.7892	1.0522	2.06E-01
	Intronic	1.1757	0.5023	3.4380	7.36E-01	1.6856	0.9747	2.9992	6.70E-02
	Intergenic	0.9742	0.7336	1.3201	8.61E-01	1.1473	0.9673	1.3625	1.16E-01
Short (<100kb)	All	1.2721	1.0750	1.5182	6.23E-03	1.0155	0.9321	1.1064	7.26E-01
	Gene-containing	1.2706	1.0205	1.6042	3.77E-02	1.1333	1.0085	1.2745	3.61E-02
	Exon-containing	1.4719	1.1164	1.9870	8.44E-03	1.2161	1.0566	1.4018	6.64E-03
	Intronic	0.9559	0.6774	1.3953	8.06E-01	0.9684	0.7883	1.1903	7.60E-01
	Intergenic	1.2856	0.9898	1.7026	6.89E-02	0.8885	0.7810	1.0107	7.21E-02

Type of Duplication	Type of CNV	RADIANT cases vs screened controls				RADIANT cases vs unscreened NBS controls			
		OR	2.50%	97.50%	p value	OR	2.50%	97.50%	p value
Long (>100kb)	All	0.9264	0.8153	1.0606	2.53E-01	0.9382	0.8696	1.0119	9.85E-02
	Gene-containing	0.9502	0.8180	1.1151	5.17E-01	0.8884	0.8156	0.9671	6.43E-03
	Exon-containing	0.9431	0.8118	1.1070	4.58E-01	0.8876	0.8146	0.9666	6.29E-03
	Intronic	Inf	NA	NA	NA	0.9660	0.3394	2.8165	9.48E-01
	Intergenic	0.8162	0.6137	1.1100	1.77E-01	1.2185	1.0047	1.4819	4.59E-02
Short (<100kb)	All	1.0419	0.8939	1.2257	6.10E-01	0.9938	0.9157	1.0784	8.81E-01
	Gene-containing	1.0559	0.8753	1.2920	5.83E-01	0.9648	0.8756	1.0625	4.67E-01
	Exon-containing	1.0521	0.8571	1.3119	6.40E-01	0.9325	0.8392	1.0350	1.91E-01
	Intronic	1.0921	0.6661	1.9180	7.42E-01	1.2533	0.9319	1.6942	1.38E-01
	Intergenic	1.0158	0.7778	1.3541	9.12E-01	1.0751	0.9183	1.2596	3.68E-01

Table S23. CNV burden in regulatory regions.

Tissues	Enhancer regions			Non-enhancer regions		
	AFF	UNAFF	LR p-value	AFF	UNAFF	LR p-value
K562 Leukemia Cells	0.0701	0.0607	0.0146	0.4362	0.4224	0.0502
All tissues combined	0.4254	0.4093	0.0240	0.0808	0.0738	0.1015
Foreskin Keratinocyte Primary Cells skin03	0.1519	0.1401	0.0262	0.3543	0.3430	0.0751
Primary B cells from peripheral blood	0.0514	0.0444	0.0398	0.4548	0.4387	0.0295
hESC Derived CD56+ Mesoderm Cultured Cells	0.1166	0.1065	0.0477	0.3896	0.3765	0.0455
Adipose Derived Mesenchymal Stem Cell Cultured Cells	0.1427	0.1328	0.0496	0.3635	0.3503	0.0514

Table S24. Regional tests on known regions associated with psychiatric disorders.

Regions (hg19)	Chr	Start	End	# Deletions in cases	# Deletions in controls	EMP1 of deletions	# Duplications in cases	# Duplications in controls	EMP1 of duplication
1q21.1	1	145,934,643	147,709,376	2	2	0.638	2	5	1.000
NRXN1	2	50,147,488	51,259,674	25	17	0.077	2	2	0.637
3q29	3	195,745,603	197,355,603	2	3	1.000	7	12	1.000
7q11.21	7	64,838,768	64,865,998	0	0	1.000	0	0	1.000
7q11.23	7	72,742,064	74,142,064	1	1	0.669	1	2	1.000
7p36.3	7	158,453,198	158,972,237	1	0	0.562	4	5	1.000
8q22.2	8	100,025,494	100,889,808	0	2	1.000	2	0	0.147
9p24.3	9	841,690	969,090	1	2	1.000	2	0	0.107
13q12.11	13	20,411,593	20,437,773	0	0	1.000	0	1	1.000
15q11.2	15	22,798,636	23,088,559	13	15	1.000	15	9	0.090
AS/PWS	15	24,820,000	28,430,000	9	6	0.149	3	1	0.243
15q13.3	15	31,132,708	32,482,708	3	6	1.000	38	34	0.270
16p13.11	16	15,510,000	16,300,000	11	19	1.000	14	18	1.000
16p11.2 distal	16	28,822,499	29,052,499	0	2	1.000	1	3	1.000
16p11.2 proximal	16	29,652,499	30,202,499	3	4	1.000	6	3	0.305
17p12	17	14,160,000	15,430,000	4	1	0.255	1	1	0.772
17q12	17	34,810,000	36,200,000	1	0	0.475	1	1	0.600
22q11.2	22	19,020,000	21,420,000	15	16	0.487	17	17	0.517

AS/PWS, Angelman/Prader–Willi syndrome

Table S25. Regional tests on known regions associated with developmental delay.

Regions (hg19)	# Deletions in cases	# Deletions in controls	EMP1 of deletions	# Duplications in cases	# Duplications in controls	EMP1 of duplication
chr1:710,137-9,977,413	34	38	0.566	62	93	1.000
chr1:860,137-3,660,140	9	19	1.000	42	67	1.000
chr1:145,338,643-147,883,376	7	8	0.641	28	25	0.326
chr1:171,733,377-172,333,377	0	0	1.000	0	0	1.000
chr1:242,433,377-246,733,377	9	8	0.415	9	14	1.000
chr1:245,033,377-248,833,377	17	24	1.000	19	29	1.000
chr2:110,000-1,720,993	7	11	1.000	5	19	1.000
chr2:3,270,993-3,470,993	0	0	1.000	0	0	1.000
chr2:45,346,496-46,046,496	2	2	0.694	6	2	0.148
chr2:111,333,937-113,133,529	1	5	1.000	3	4	1.000
chr2:111,333,937-113,233,529	1	5	1.000	3	4	1.000
chr2:165,691,754-166,391,754	0	2	1.000	0	1	1.000
chr2:235,735,261-243,102,476	11	4	0.032	49	40	0.120
chr3:125,000-925,000	8	8	0.389	7	8	0.569
chr3:825,000-1,425,000	6	3	0.165	10	7	0.405
chr3:2,125,000-9,825,000	129	106	0.005	17	14	0.368
chr3:195,715,603-197,415,603	2	3	1.000	7	12	1.000
chr4:110,000-7,049,099	50	35	0.031	42	51	1.000
chr4:360,000-3,913,620	10	9	0.327	37	45	1.000
chr4:9,840,902-10,841,902	5	7	1.000	0	7	1.000
chr4:81,730,976-83,130,976	0	0	1.000	0	4	1.000
chr4:184,013,006-184,513,006	0	0	1.000	0	1	1.000
chr4:187,263,006-187,963,006	0	3	1.000	2	1	0.452
chr5:47,000-1,447,000	6	8	1.000	44	40	0.192
chr5:3,697,000-4,397,000	0	0	1.000	3	1	0.216
chr5:175,517,394-177,517,394	25	18	0.093	3	5	1.000
chr5:180,117,394-180,817,394	1	1	0.818	27	26	0.389
chr6:155,000-5,855,001	24	34	1.000	18	33	1.000
chr6:20,742,021-21,142,021	2	0	0.150	1	0	0.584
chr6:165,330,010-170,908,075	9	6	0.213	11	23	1.000
chr7:10,239-3,833,474	27	36	1.000	23	27	1.000
chr7:5,733,474-6,233,475	2	1	0.276	6	2	0.179
chr7:72,662,064-74,262,064	1	1	0.670	1	2	1.000
chr8:160,000-11,912,591	180	191	0.196	84	104	1.000
chr8:360,000-1,062,593	3	5	1.000	5	3	0.207
chr8:2,362,593-4,362,592	39	30	0.050	5	6	1.000
chr8:8,212,590-11,912,591	17	36	1.000	10	12	1.000
chr8:53,287,447-53,887,447	0	0	1.000	6	19	1.000
chr8:143,252,093-145,979,195	26	15	0.055	34	60	1.000
chr9:160,000-1,660,000	32	41	1.000	46	54	1.000
chr9:160,000-6,760,000	74	83	0.452	66	77	1.000
chr9:131,060,179-141,080,179	13	13	0.503	47	60	1.000

Regions (hg19)	# Deletions in cases	# Deletions in controls	EMP1 of deletions	# Duplications in cases	# Duplications in controls	EMP1 of duplication
chr10:2,610,000-3,210,000	0	3	1.000	2	5	1.000
chr10:81,610,020-88,910,020	16	21	1.000	31	24	0.072
chr10:127,760,010-135,400,010	7	11	1.000	20	28	1.000
chr11:310,000-3,443,424	7	7	0.509	9	14	1.000
chr11:128,044,790-134,844,790	14	21	1.000	72	77	0.313
chr12:229,739-3,629,739	15	13	0.330	20	24	1.000
chr12:279,739-779,739	5	4	0.441	3	2	0.585
chr12:8,158,733-8,358,733	0	1	1.000	0	0	1.000
chr13:19,402,000-20,302,000	0	1	1.000	6	6	0.504
chr14:36,430,249-37,230,249	0	0	1.000	3	0	0.122
chr14:104,480,247-106,378,955	15	3	0.004	44	20	0.002
chr15:22,648,636-28,626,405	49	50	0.145	46	38	0.082
chr15:22,648,636-31,912,708	59	63	0.200	61	53	0.112
chr15:30,862,708-32,962,708	10	10	0.489	38	35	0.316
chr15:85,098,996-85,798,996	9	3	0.063	4	2	0.294
chr15:100,382,477-102,382,477	12	16	1.000	55	54	0.355
chr15:101,032,477-101,732,477	5	1	0.093	3	1	0.299
chr16:160,000-5,209,999	15	24	1.000	41	34	0.093
chr16:709,999-2,509,999	6	0	0.009	13	10	0.208
chr16:3,709,999-5,209,999	7	20	1.000	1	2	1.000
chr16:14,892,499-16,912,499	24	32	1.000	35	42	1.000
chr16:14,892,499-18,292,499	24	32	1.000	37	44	1.000
chr16:21,892,499-22,492,499	5	4	0.458	2	6	1.000
chr16:28,442,499-30,342,499	5	6	1.000	9	8	0.511
chr16:83,792,499-90,222,499	35	30	0.218	18	24	1.000
chr16:87,742,499-90,172,499	8	11	1.000	14	11	0.240
chr17:100,000-4,153,251	16	27	1.000	21	29	1.000
chr17:703,250-1,603,250	4	3	0.527	17	14	0.275
chr17:16,659,275-25,475,873	40	24	0.008	23	40	1.000
chr17:16,709,275-20,309,408	24	11	0.010	6	8	1.000
chr17:29,025,874-29,825,880	0	4	1.000	4	0	0.087
chr17:34,725,887-36,295,000	1	0	0.473	2	2	0.581
chr17:34,775,887-36,275,614	1	0	0.473	2	2	0.581
chr17:43,644,217-44,144,178	0	0	1.000	3	2	0.497
chr17:72,088,405-81,060,000	7	10	1.000	46	53	1.000
chr18:110,000-5,310,000	61	57	0.137	10	17	1.000
chr18:6,760,000-7,360,000	0	1	1.000	2	2	0.638
chr18:70,949,020-77,899,009	9	16	1.000	27	15	0.025
chr19:199,000-5,899,000	5	9	1.000	41	34	0.060
chr19:199,000-8,789,000	19	27	1.000	75	82	0.344
chr19:54,858,188-59,058,188	10	18	1.000	20	38	1.000
chr20:152,000-1,162,000	2	1	0.507	6	7	1.000
chr21:21,028,129-21,328,129	20	14	0.060	1	0	0.563
chr21:42,478,130-47,975,572	7	11	1.000	20	24	1.000

Regions (hg19)	# Deletions in cases	# Deletions in controls	EMP1 of deletions	# Duplications in cases	# Duplications in controls	EMP1 of duplication
chr22:17,470,000-25,020,000	48	43	0.157	39	39	0.505
chr22:18,820,000-22,270,000	41	41	0.318	27	26	0.385
chr22:23,370,000-23,770,000	0	0	1.000	0	0	1.000
chr22:25,370,000-26,170,000	1	0	0.476	2	2	0.557
chr22:44,268,667-51,244,566	19	39	1.000	25	27	0.267
chr22:47,021,336-51,244,566	14	29	1.000	19	23	1.000

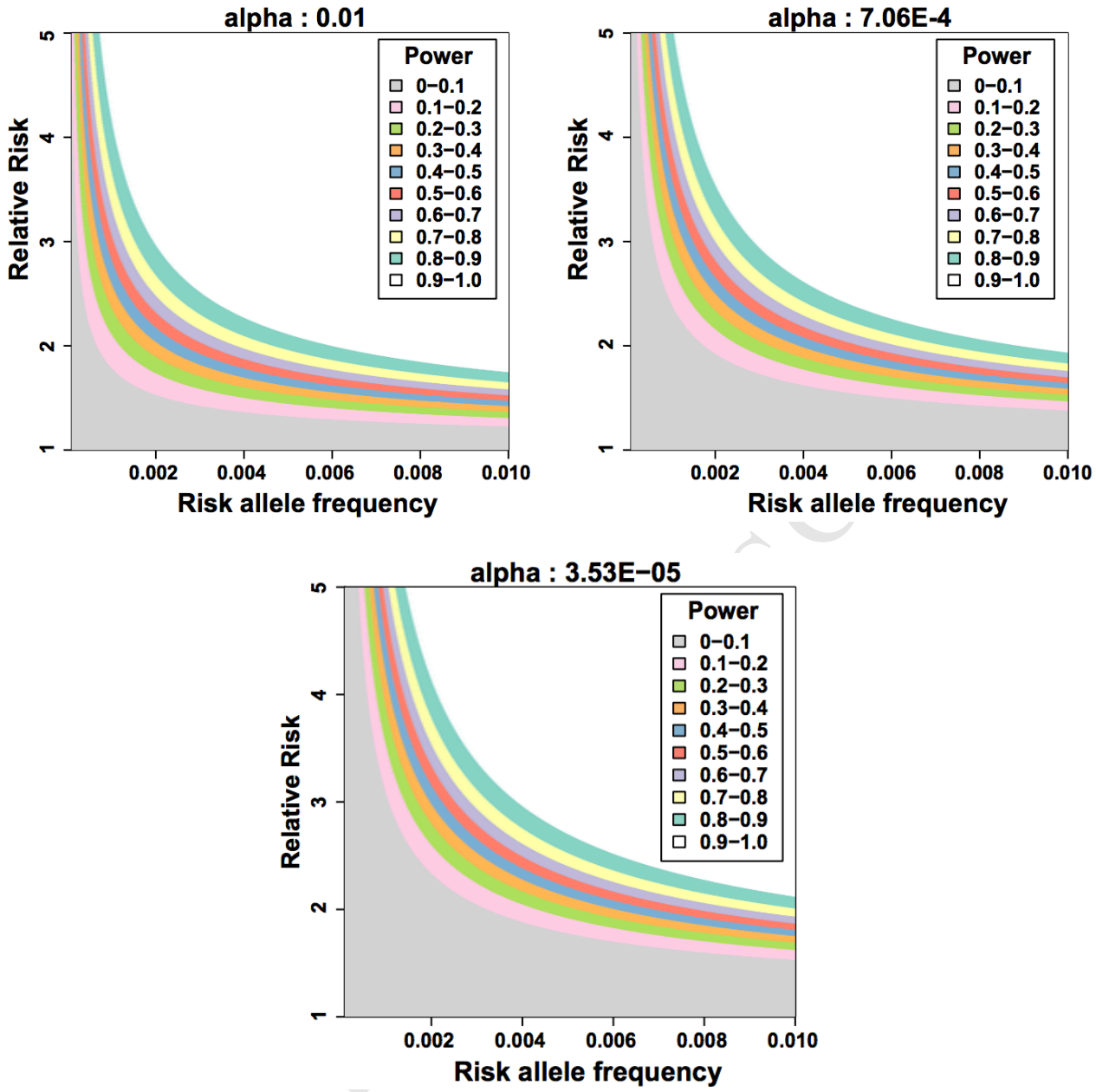


Figure S1. Statistical power to detect single CNV loci associated with MDD. Different colors represent different power intervals over the genotypic relative risk (y axis) and the risk allele frequency in the population (x axis). Calculations were based on 5780 cases, 6626 controls, a dominant model, lifetime risk of MDD of 10% and at three levels of α (0.05, 7.06E-04, 3.53E-05).

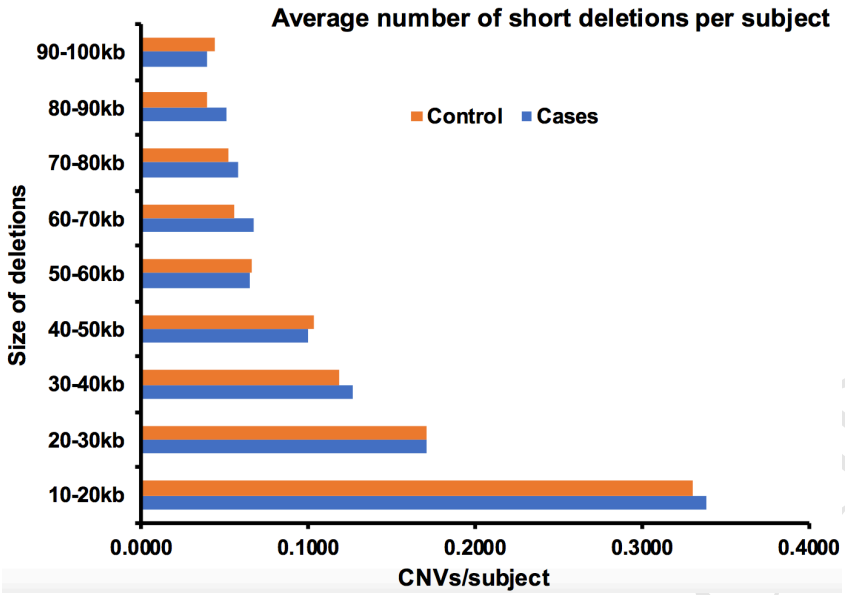


Figure S2. Average number of short deletions of various sizes per subject.

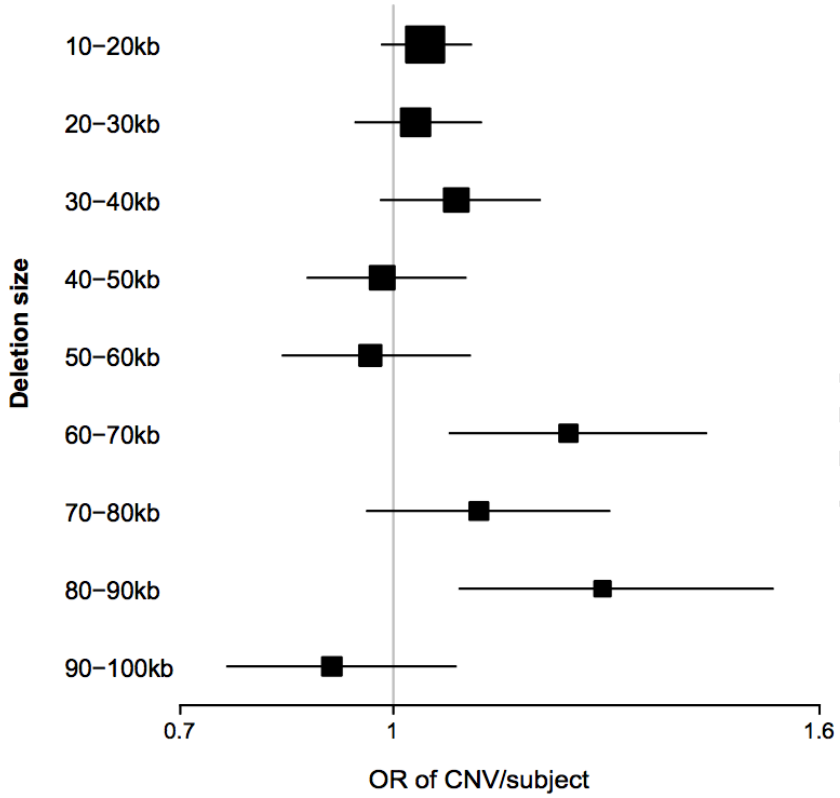


Figure S3. Odds ratios and 95% confidence intervals of short deletions of various sizes. The size of the square is proportional to precision.

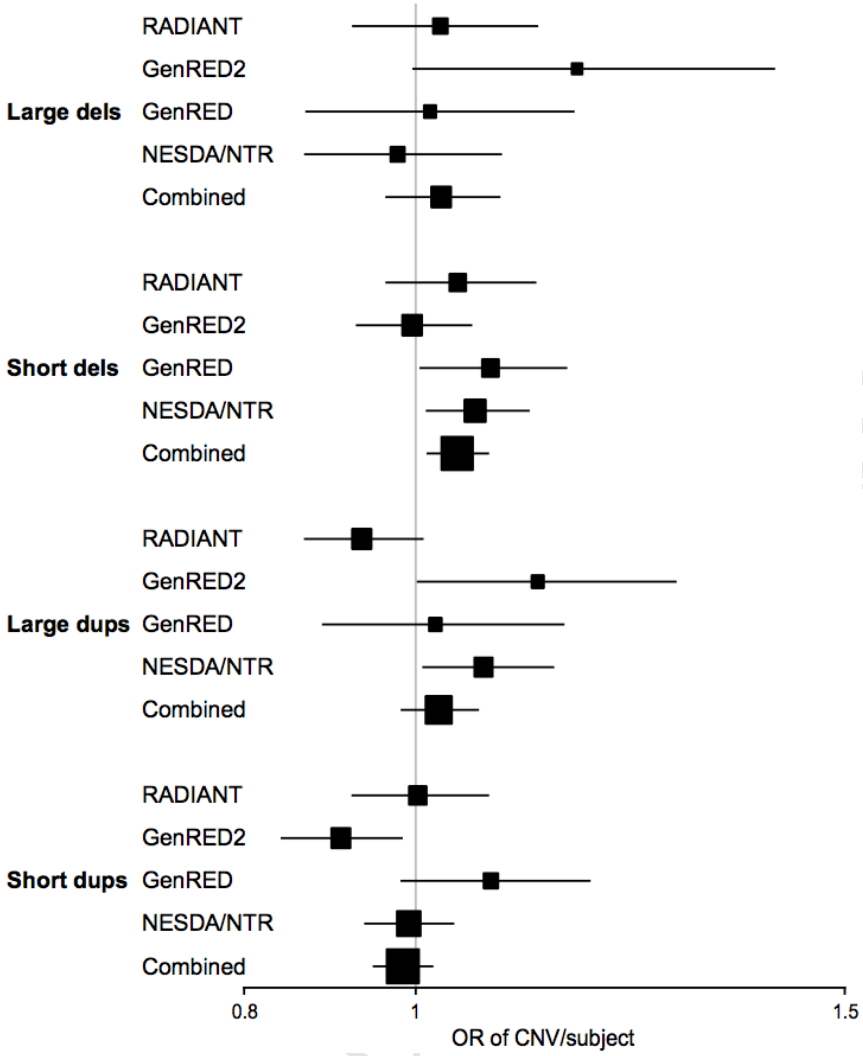


Figure S4. The forest plot of odds ratio (OR) estimates and 95% confidence intervals for each burden test by cohort.

Figure S5. Plots of 15q11.2 dups, 6q21 dups, 8p22 dels, and 6q26 dels

Shown below are plots of CNVs in the four independent regions listed in Table 3, for both case and control carriers. All CNVs in the dataset are shown for 15q11.2 duplications, 6q21 duplications. For the more frequent CNVs, 15 CNVs were randomly selected from among the 92 8p22 deletions and 15 from among the 105 6q26 deletions. Plots of all CNVs in these regions, and for randomly selected negative controls, are available on request.

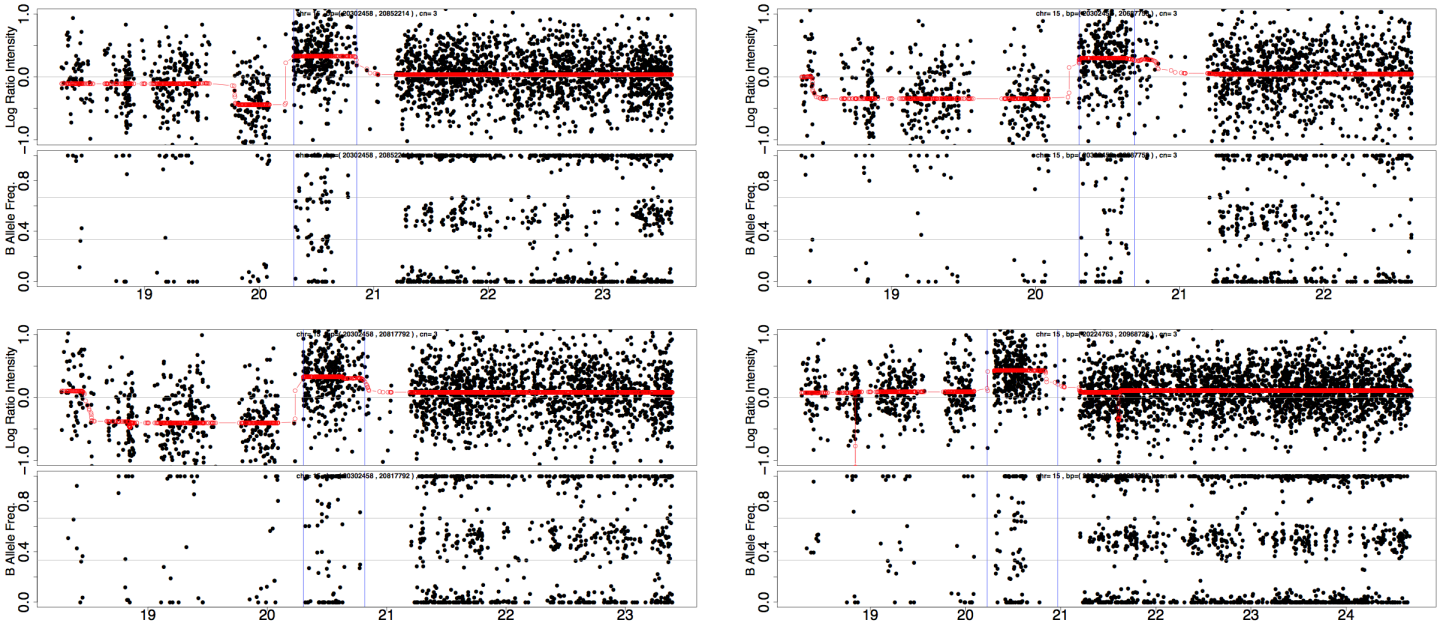
In each plot, the copy number and the position of the CNV boundaries are shown in the top, as called by Birdsuite for Affymetrix data or QuantiSNP for Illumina data. The physical positions of CNVs in the ***GenRED-II*** cohort are based on hg19 while the positions for all the other cohorts are based on hg18 (although for statistical analyses in this paper, all hg18 coordinates were lifted over to hg19).

X-axis values are bp locations. Y-axis values are Log R Ratio [LRR] (upper panels) and B Allele Frequency [BAF] (lower panels). Blue vertical lines represent the CNV boundaries reported by Birdsuite for Affymetrix data or QuantiSNP for Illumina data. The red dots are the point-by-point copy number estimates made by an alternative algorithm (Lai et al., 2008).

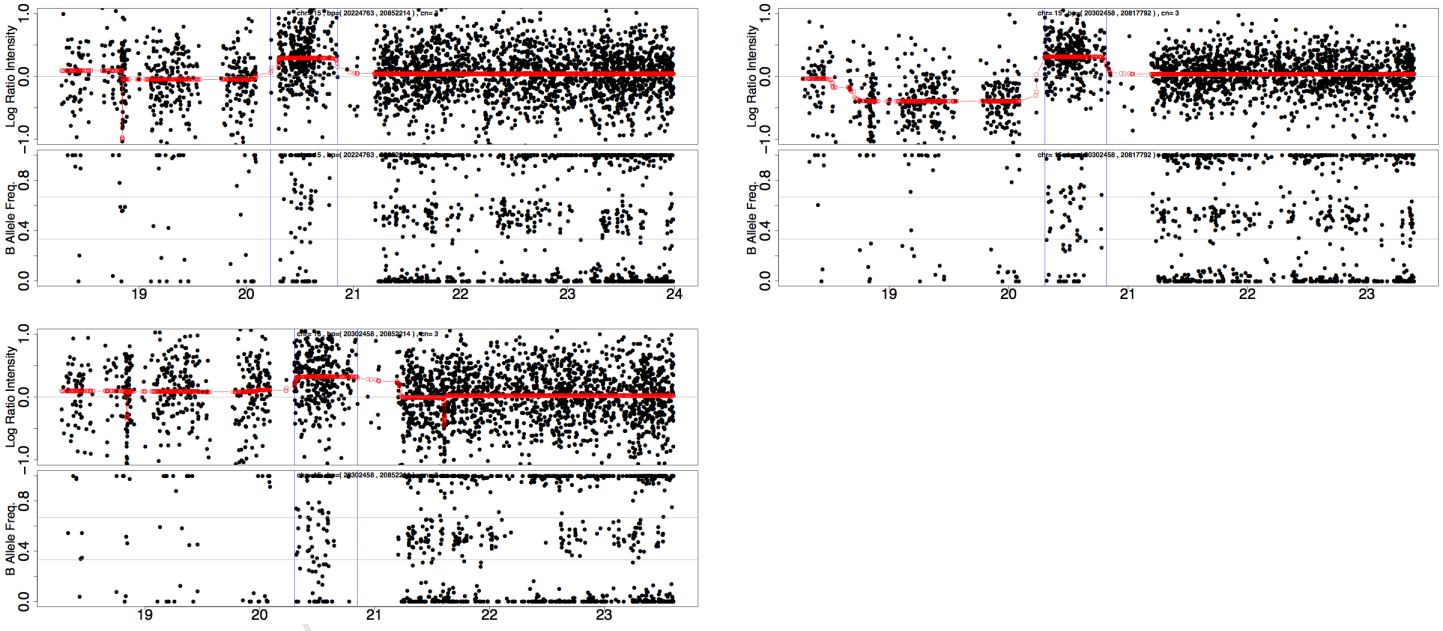
Lai TL, Xing H, Zhang N (2008): Stochastic segmentation models for array-based comparative genomic hybridization data analysis. Biostatistics. 9:290-307.

(A) All the duplications in chromosome 15q11.2

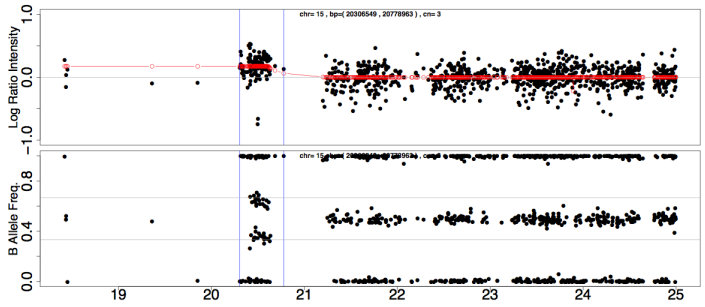
NESDA/NTR Case duplication (hg18)

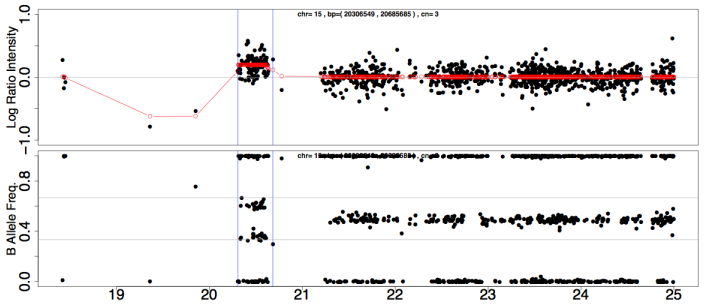


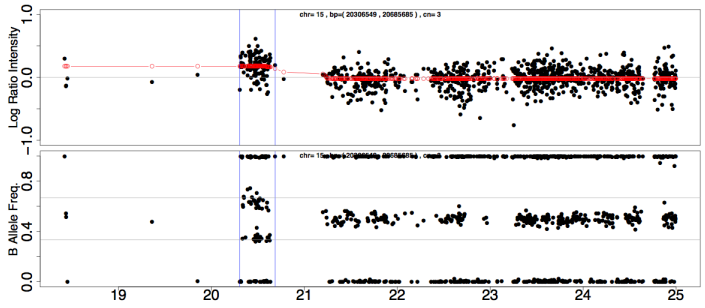
NESDA/NTR Control duplication (hg18)

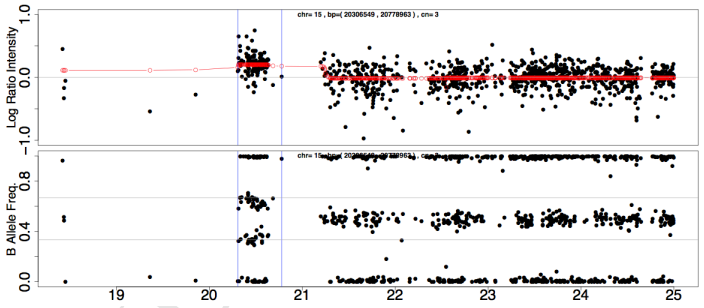


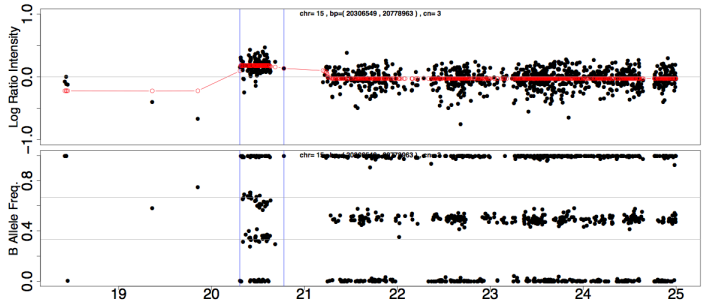
RADIANT Case duplication (hg18)

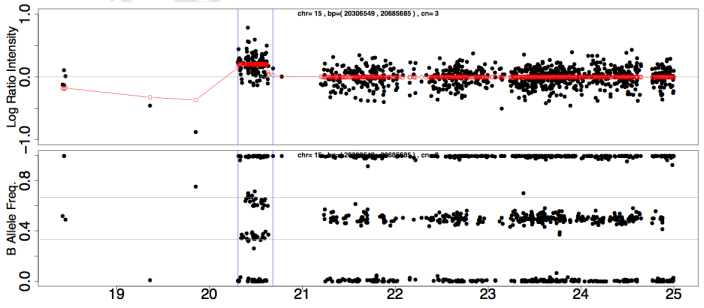


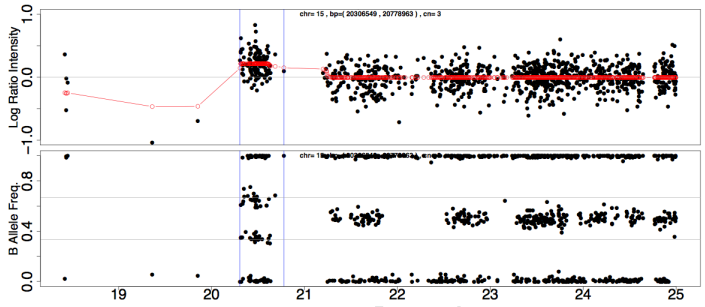




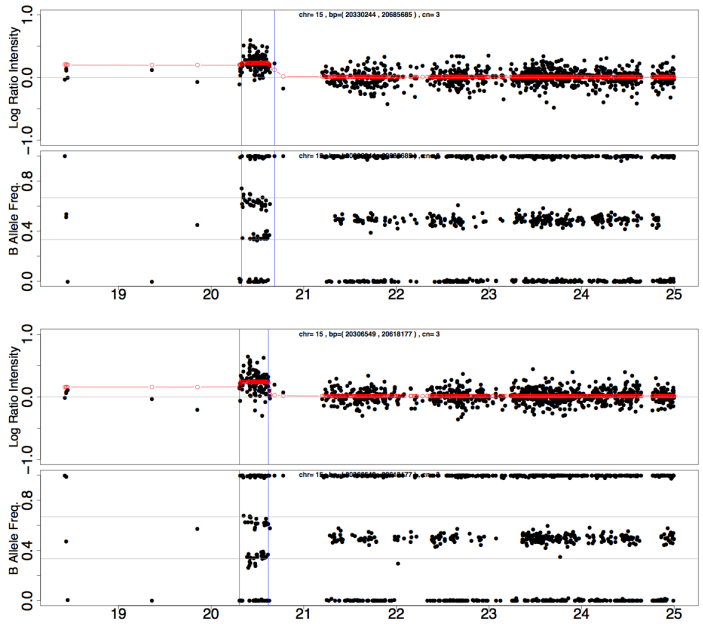


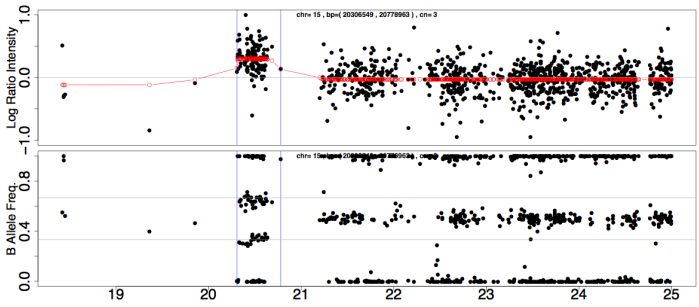




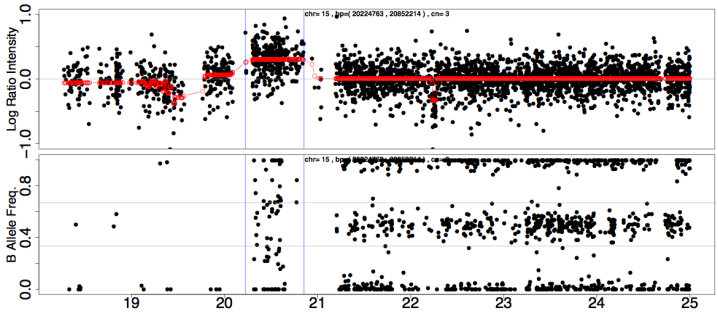


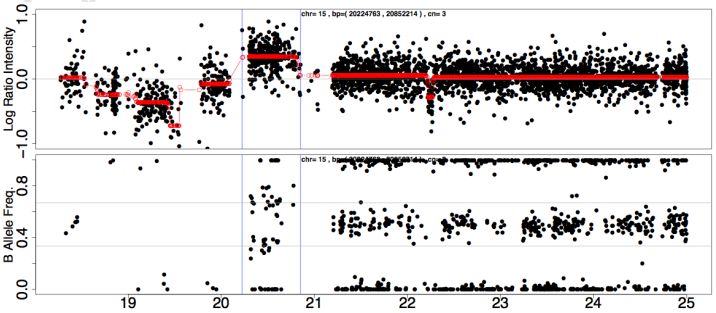
RADIANT Control duplication (hg18)



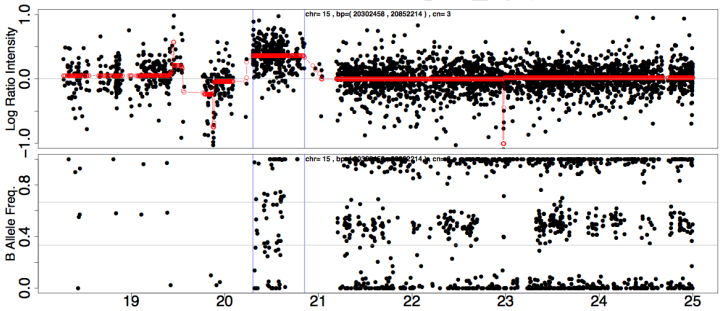


GenRED Case duplication (hg18)

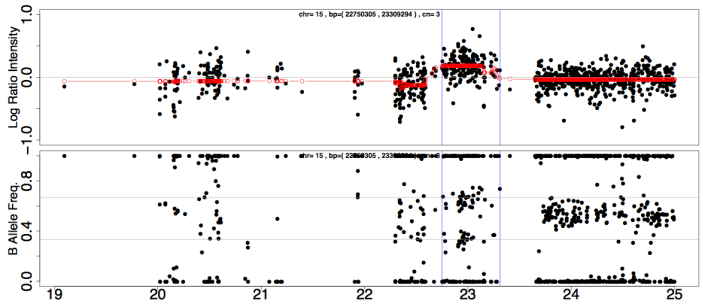


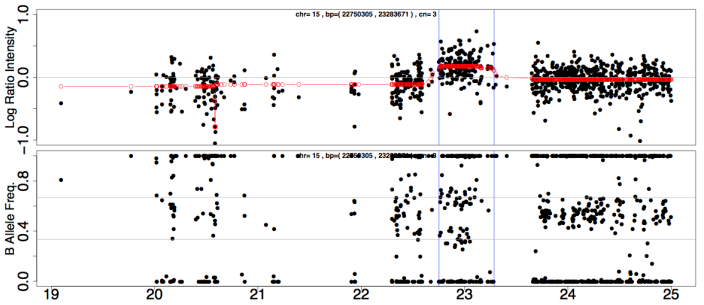


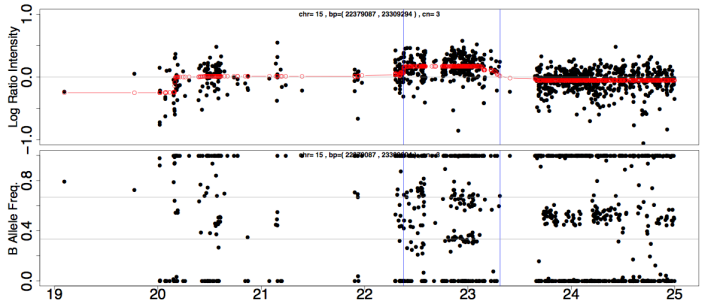
GenRED Control duplication (hg18)

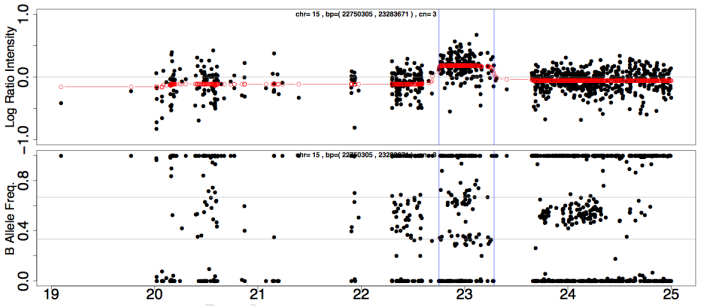


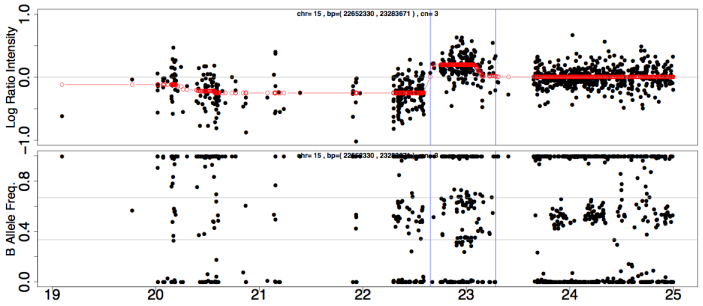
GenRED-II Case duplication (hg19)

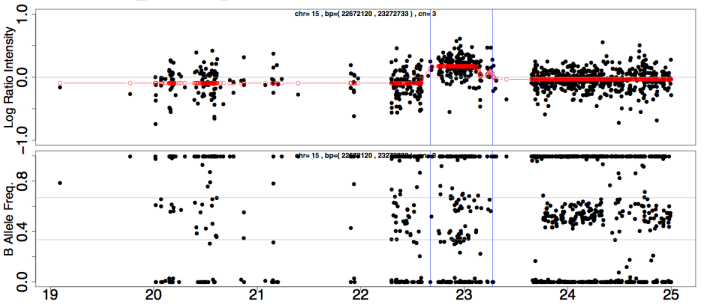


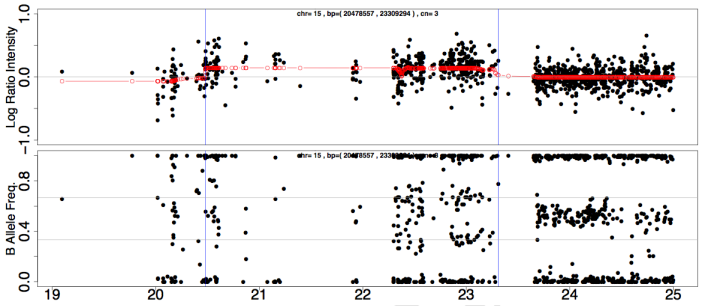


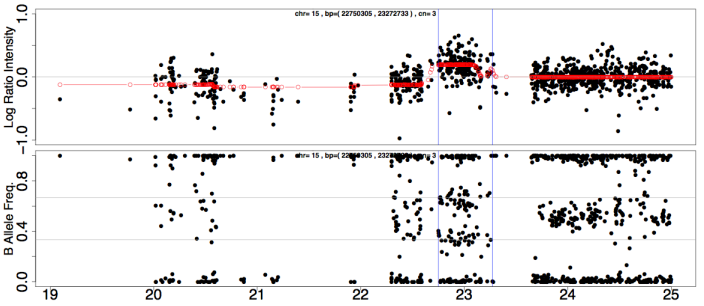


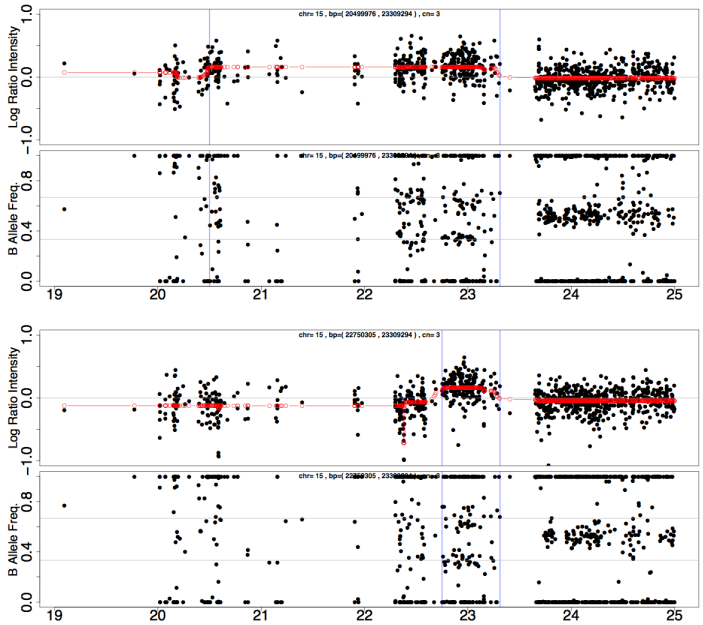


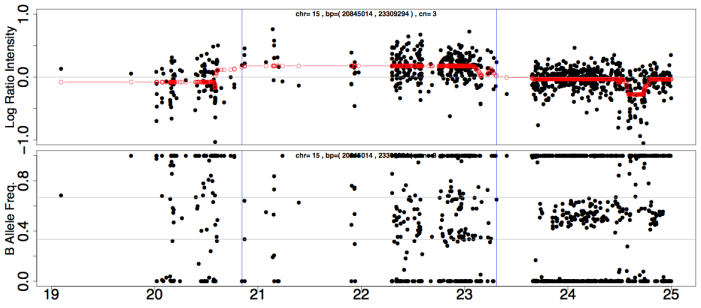






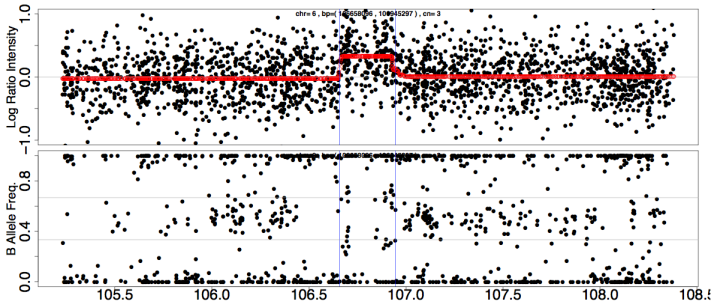


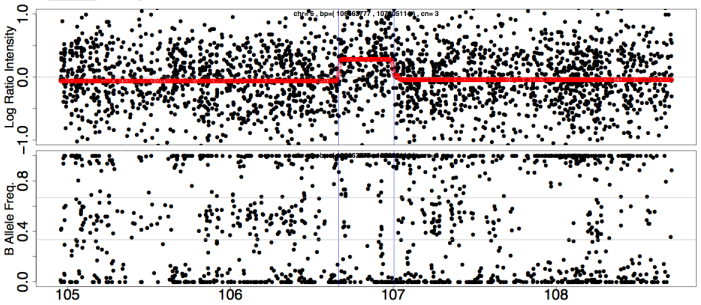


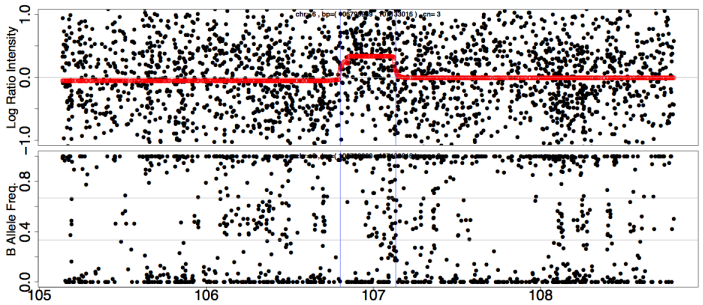


(B) All the duplications in chromosome 6q21

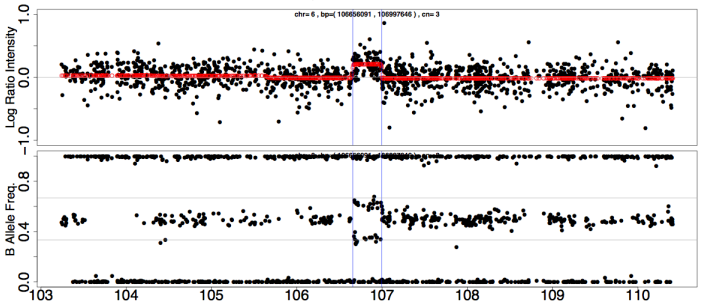
NESDA/NTR Case duplication (hg18)

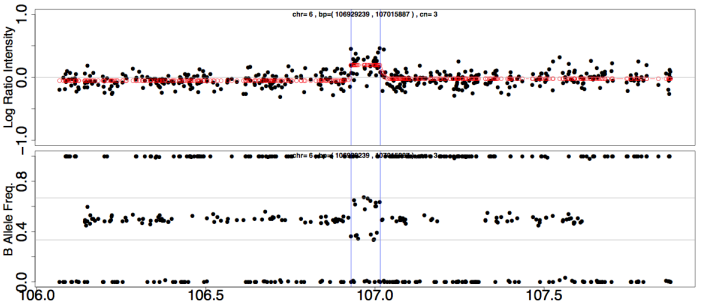




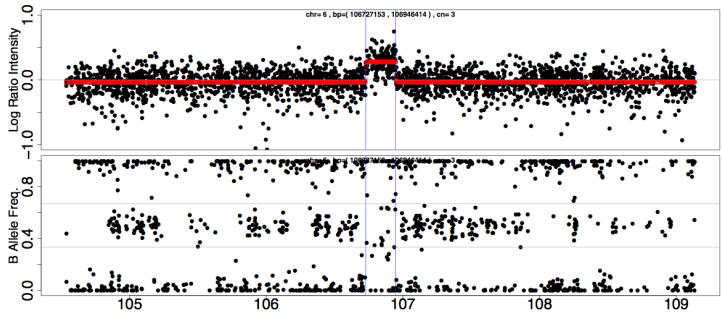


RADIANT Case duplication (hg18)



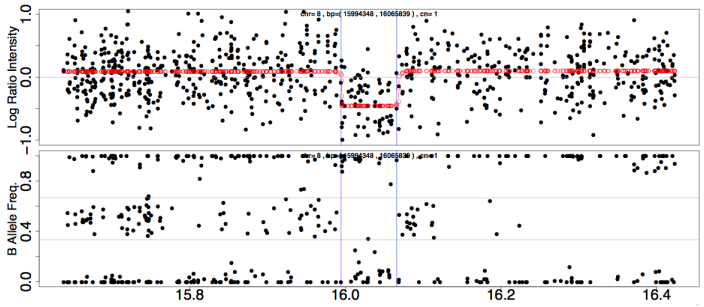


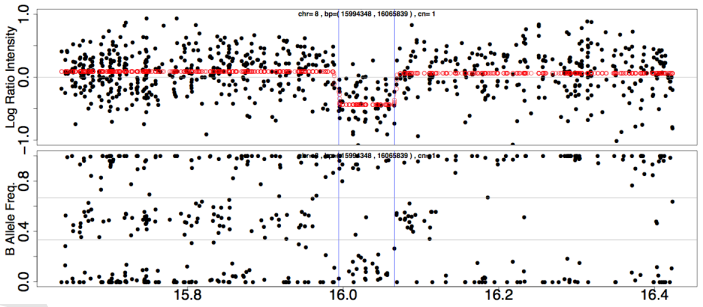
GenRED Case duplication (hg18)



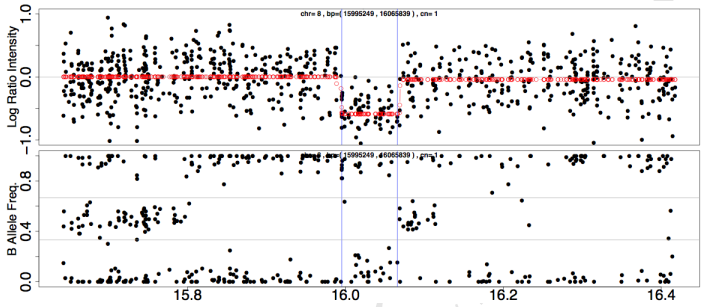
(C) Examples of deletions in chromosome 8p22

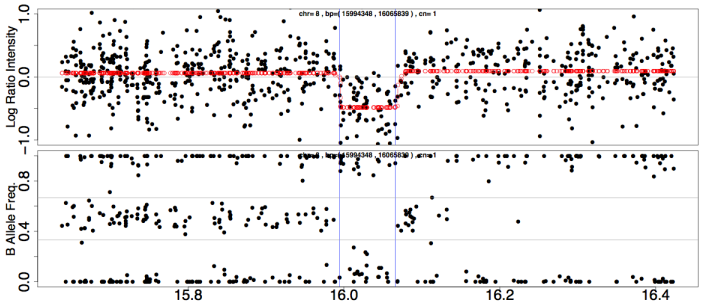
NESDA/NTR Case deletion (hg18)



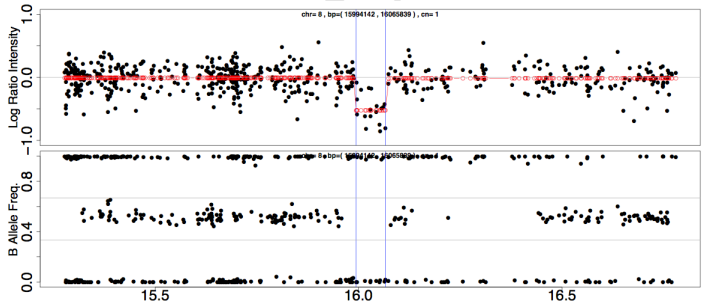


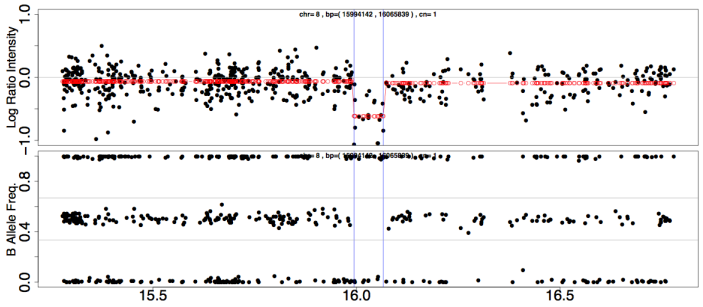
NESDA/NTR Control deletion (hg18)



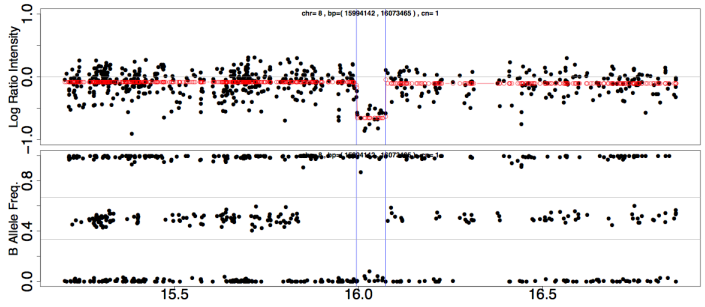


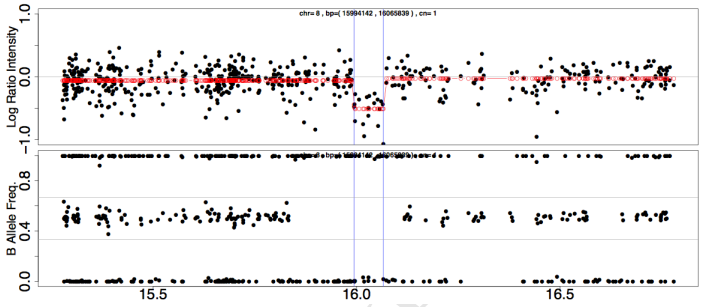
RADIANT Case deletion (hg18)



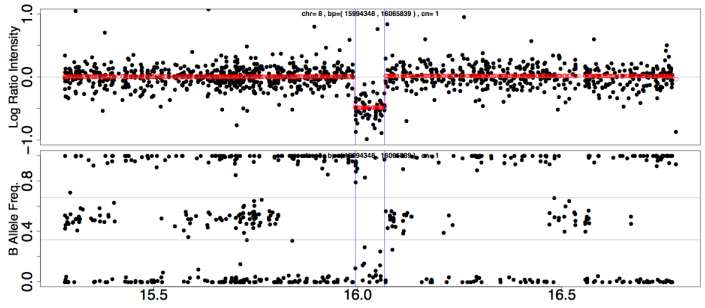


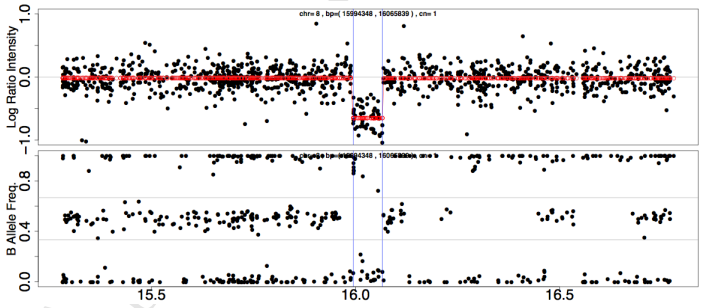
RADIANT Control deletion (hg18)



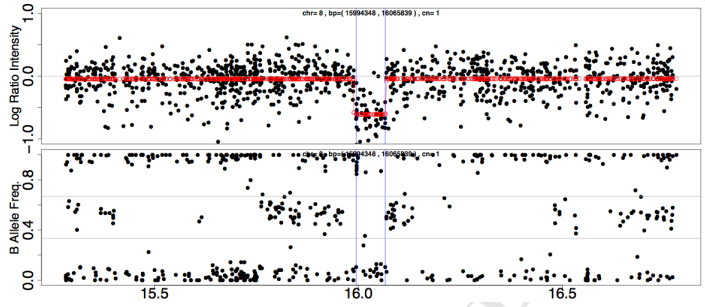


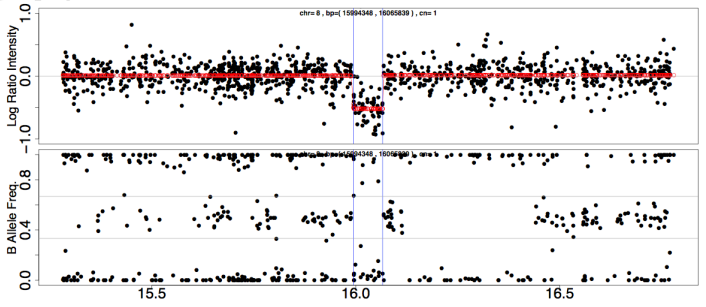
GenRED Case deletion (hg18)



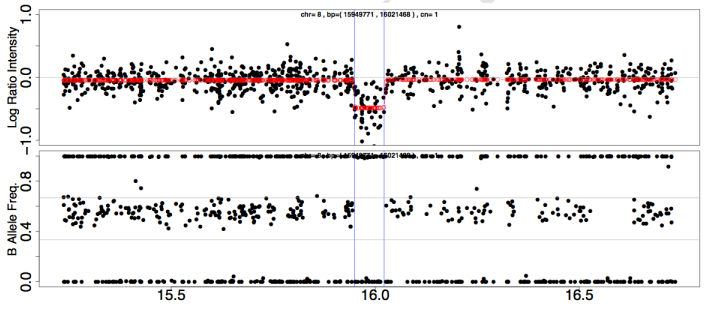


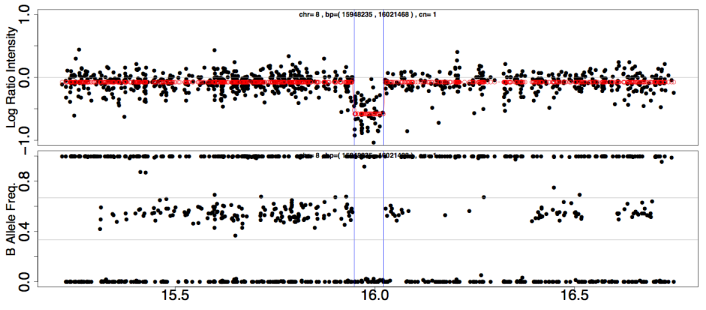
GenRED Control deletion (hg18)



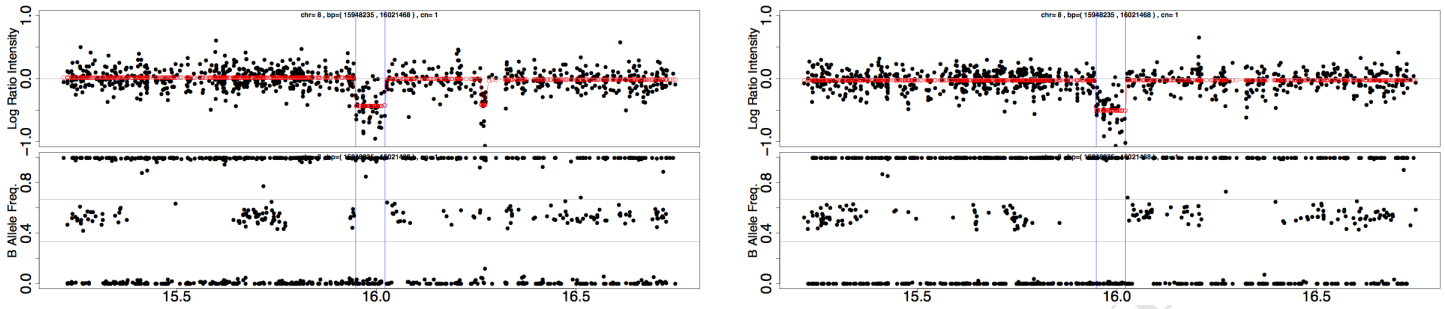


GenRED-II Case deletion (hg19)



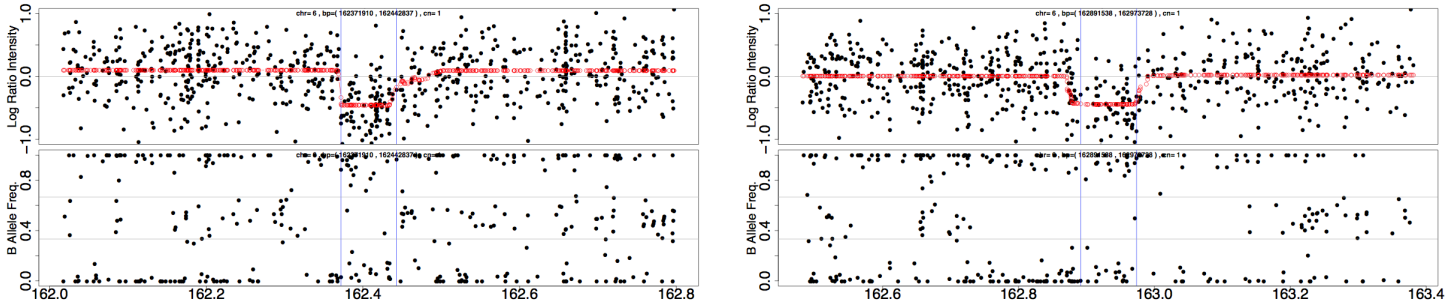


GenRED-II Control deletion (hg19)

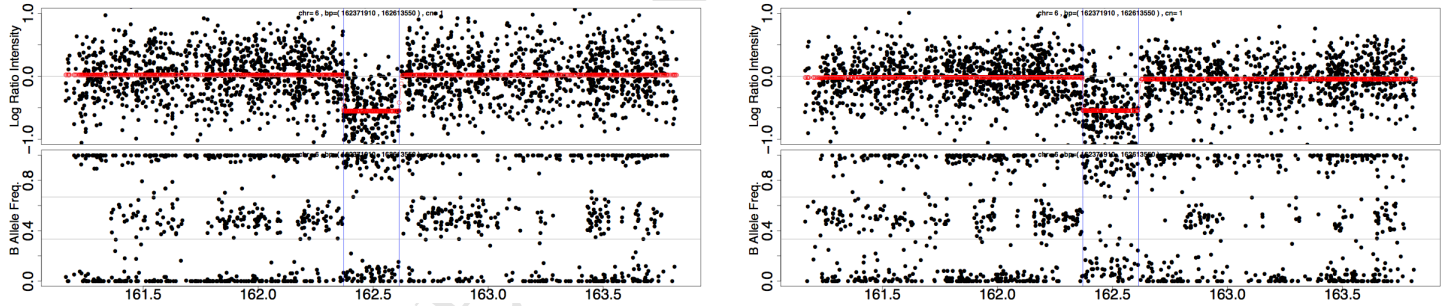


(D) Examples of deletions in chromosome 6q26

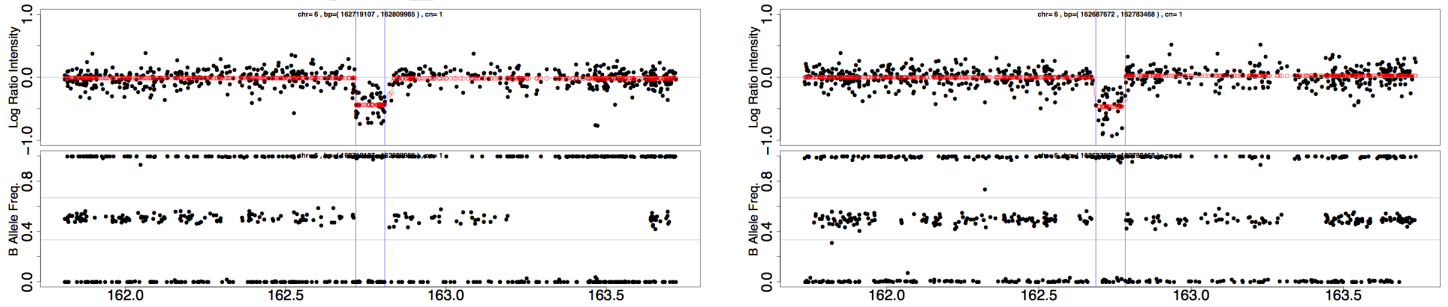
NESDA/NTR Case deletion (hg18)



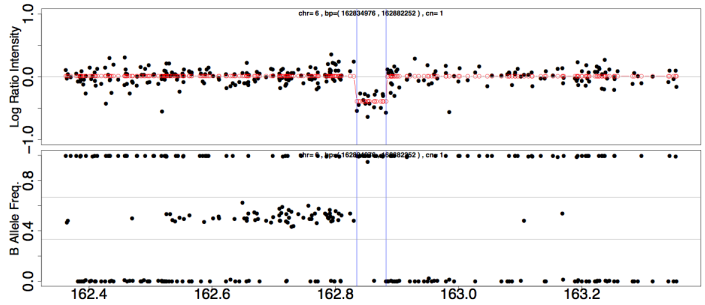
NESDA/NTR Control deletion (hg18)

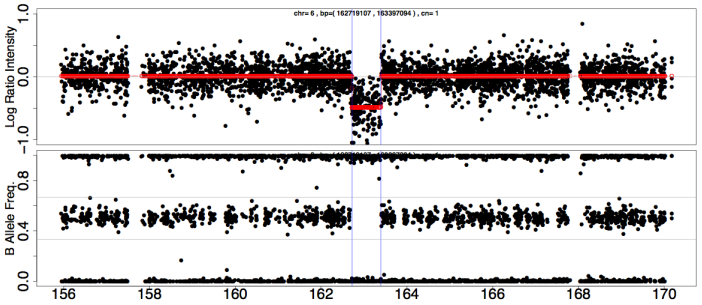


RADIANT Case deletion (hg18)

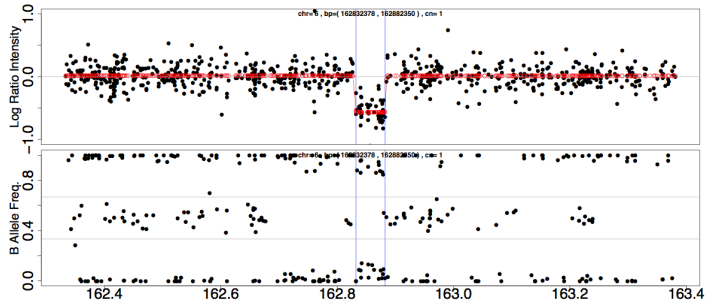


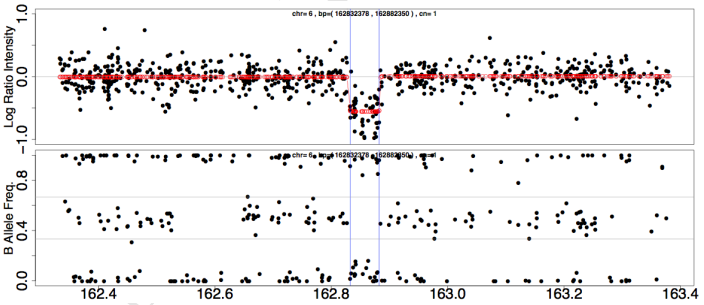
RADIANT Control deletion (hg18)



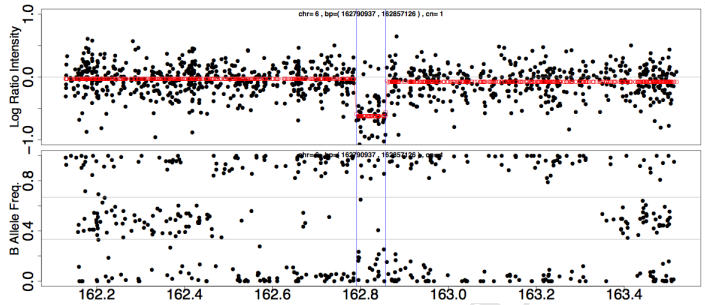


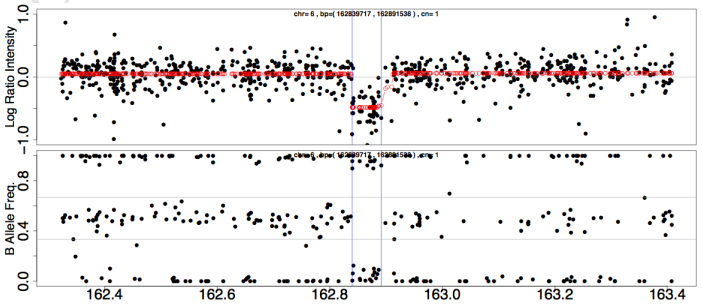
GenRED Case deletion (hg18)



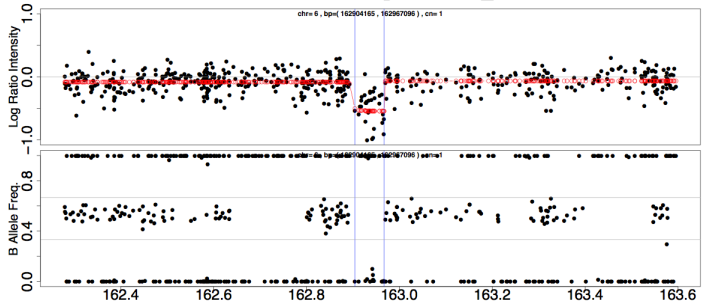


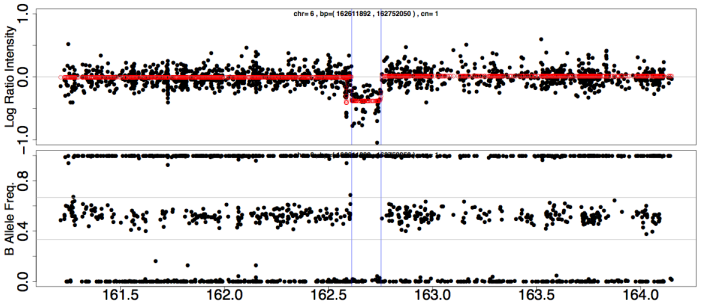
GenRED Control deletion (hg18)



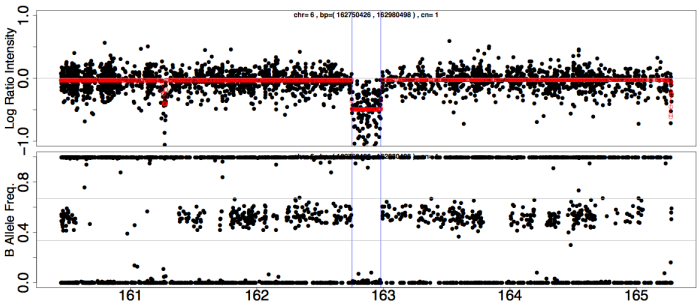


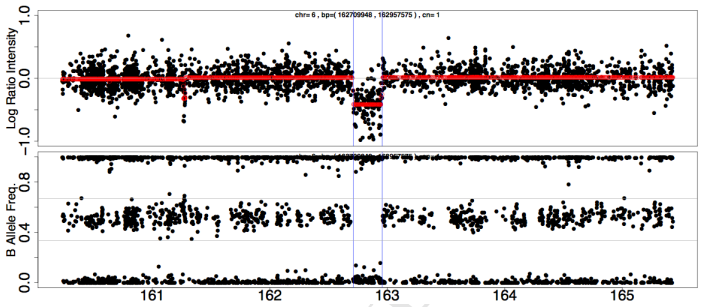
GenRED-II Case deletion (hg19)





GenRED-II Control deletion (hg19)





Codes for the analysis pipeline: PLINK command and R scripts used in the analyses

```
##########################################################################
Permutation test for global burden of rare CNV
##########################################################################

# Exonic deletions
plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-del \
--cnv-kb 100 \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--cnv-count hg19_Exons.txt \
--out Del_100kb_exon_count

plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-del \
--cnv-kb 100 \
--cnv-freq-exclude-above 1 \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--cnv-count hg19_Exons.txt \
--out Del_100kb_singleton_exon_count

plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-del \
--cnv-kb 500 \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--cnv-count hg19_Exons.txt \
--out Del_500kb_exon_count

plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-del \
--cnv-kb 1000 \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--cnv-count hg19_Exons.txt \
--out Del_1000kb_exon_count

plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-del \
--cnv-kb 9 \
--cnv-max-kb 100 \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
```

```
--cnv-count hg19_Exons.txt \
--out Del_small_exon_count

plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-del \
--cnv-kb 9 \
--cnv-max-kb 100 \
--cnv-freq-exclude-above 1 \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--cnv-count hg19_Exons.txt \
--out Del_small_singleton_exon_count

plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-del \
--cnv-kb 100 \
--cnv-intersect hg19_Exons.txt \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--out Del_100_exon_intersect

plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-del \
--cnv-kb 100 \
--cnv-freq-exclude-above 1 \
--cnv-intersect hg19_Exons.txt \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--out Del_100_singleton_exon_intersect

plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-del \
--cnv-kb 500 \
--cnv-intersect hg19_Exons.txt \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--out Del_500_exon_intersect

plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-del \
--cnv-kb 1000 \
--cnv-intersect hg19_Exons.txt \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--out Del_1000_exon_intersect

plink --noweb \
```

```
--cfile Filter_Rare_CNV \
--cnv-del \
--cnv-kb 9 \
--cnv-max-kb 100 \
--cnv-intersect hg19_Exons.txt \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--out Del_small_exon_intersect

plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-del \
--cnv-kb 9 \
--cnv-max-kb 100 \
--cnv-freq-exclude-above 1 \
--cnv-intersect hg19_Exons.txt \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--out Del_small_singleton_exon_intersect

# Genic deletions
plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-del \
--cnv-kb 100 \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--cnv-count hg19_RefGenes.txt \
--out Del_100kb_gene_count

plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-del \
--cnv-kb 100 \
--cnv-freq-exclude-above 1 \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--cnv-count hg19_RefGenes.txt \
--out Del_100kb_singleton_gene_count

plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-del \
--cnv-kb 500 \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--cnv-count hg19_RefGenes.txt \
--out Del_500kb_gene_count

plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-del \
```

```
--cnv-kb 1000 \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--cnv-count hg19_RefGenes.txt \
--out Del_1000kb_gene_count

plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-del \
--cnv-kb 9 \
--cnv-max-kb 100 \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--cnv-count hg19_RefGenes.txt \
--out Del_small_gene_count

plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-del \
--cnv-kb 9 \
--cnv-max-kb 100 \
--cnv-freq-exclude-above 1 \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--cnv-count hg19_RefGenes.txt \
--out Del_small_singleton_gene_count

plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-del \
--cnv-kb 100 \
--cnv-intersect hg19_RefGenes.txt \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--out Del_100_gene_intersect

plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-del \
--cnv-kb 100 \
--cnv-freq-exclude-above 1 \
--cnv-intersect hg19_RefGenes.txt \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--out Del_100_singleton_gene_intersect

plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-del \
--cnv-kb 500 \
--cnv-intersect hg19_RefGenes.txt \
--cnv-indiv-perm \
```

```
--mperm 100000 --within Sex_Batch_cluster.txt \
--out Del_500_gene_intersect

plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-del \
--cnv-kb 1000 \
--cnv-intersect hg19_RefGenes.txt \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--out Del_1000_gene_intersect

plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-del \
--cnv-kb 9 \
--cnv-max-kb 100 \
--cnv-intersect hg19_RefGenes.txt \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--out Del_small_gene_intersect

plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-del \
--cnv-kb 9 \
--cnv-max-kb 100 \
--cnv-freq-exclude-above 1 \
--cnv-intersect hg19_RefGenes.txt \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--out Del_small_singleton_gene_intersect

# Exonic duplications
plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-dup \
--cnv-kb 100 \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--cnv-count hg19_Exons.txt \
--out Dup_100kb_exon_count

plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-dup \
--cnv-kb 100 \
--cnv-freq-exclude-above 1 \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--cnv-count hg19_Exons.txt \
--out Dup_100kb_singleton_exon_count
```

```
plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-dup \
--cnv-kb 500 \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--cnv-count hg19_Exons.txt \
--out Dup_500kb_exon_count

plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-dup \
--cnv-kb 1000 \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--cnv-count hg19_Exons.txt \
--out Dup_1000kb_exon_count

plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-dup \
--cnv-kb 9 \
--cnv-max-kb 100 \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--cnv-count hg19_Exons.txt \
--out Dup_small_exon_count

plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-dup \
--cnv-kb 9 \
--cnv-max-kb 100 \
--cnv-freq-exclude-above 1 \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--cnv-count hg19_Exons.txt \
--out Dup_small_singleton_exon_count

plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-dup \
--cnv-kb 100 \
--cnv-intersect hg19_Exons.txt \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--out Dup_100_exon_intersect

plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-dup \
```

```
--cnv-kb 100 \
--cnv-freq-exclude-above 1 \
--cnv-intersect hg19_Exons.txt \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--out Dup_100_singleton_exon_intersect

plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-dup \
--cnv-kb 500 \
--cnv-intersect hg19_Exons.txt \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--out Dup_500_exon_intersect

plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-dup \
--cnv-kb 1000 \
--cnv-intersect hg19_Exons.txt \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--out Dup_1000_exon_intersect

plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-dup \
--cnv-kb 9 \
--cnv-max-kb 100 \
--cnv-intersect hg19_Exons.txt \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--out Dup_small_exon_intersect

plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-dup \
--cnv-kb 9 \
--cnv-max-kb 100 \
--cnv-freq-exclude-above 1 \
--cnv-intersect hg19_Exons.txt \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--out Dup_small_singleton_exon_intersect

# Genic duplications
plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-dup \
--cnv-kb 100 \
--cnv-indiv-perm \
```

```
--mperm 100000 --within Sex_Batch_cluster.txt \
--cnv-count hg19_RefGenes.txt \
--out Dup_100kb_gene_count

plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-dup \
--cnv-kb 100 \
--cnv-freq-exclude-above 1 \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--cnv-count hg19_RefGenes.txt \
--out Dup_100kb_singleton_gene_count

plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-dup \
--cnv-kb 500 \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--cnv-count hg19_RefGenes.txt \
--out Dup_500kb_gene_count

plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-dup \
--cnv-kb 1000 \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--cnv-count hg19_RefGenes.txt \
--out Dup_1000kb_gene_count

plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-dup \
--cnv-kb 9 \
--cnv-max-kb 100 \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--cnv-count hg19_RefGenes.txt \
--out Dup_small_gene_count

plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-dup \
--cnv-kb 9 \
--cnv-max-kb 100 \
--cnv-freq-exclude-above 1 \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--cnv-count hg19_RefGenes.txt \
--out Dup_small_singleton_gene_count
```

```
plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-dup \
--cnv-kb 100 \
--cnv-intersect hg19_RefGenes.txt \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--out Dup_100_gene_intersect

plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-dup \
--cnv-kb 100 \
--cnv-freq-exclude-above 1 \
--cnv-intersect hg19_RefGenes.txt \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--out Dup_100_singleton_gene_intersect

plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-dup \
--cnv-kb 500 \
--cnv-intersect hg19_RefGenes.txt \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--out Dup_500_gene_intersect

plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-dup \
--cnv-kb 1000 \
--cnv-intersect hg19_RefGenes.txt \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--out Dup_1000_gene_intersect

plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-dup \
--cnv-kb 9 \
--cnv-max-kb 100 \
--cnv-intersect hg19_RefGenes.txt \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--out Dup_small_gene_intersect

plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-dup \
--cnv-kb 9 \
```

```
--cnv-max-kb 100 \
--cnv-freq-exclude-above 1 \
--cnv-intersect hg19_RefGenes.txt \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--out Dup_small_singleton_gene_intersect

# Intergenic duplications
plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-dup \
--cnv-kb 100 \
--cnv-exclude hg19_RefGenes.txt \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--out Dup_100_intergenic

plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-dup \
--cnv-kb 100 \
--cnv-freq-exclude-above 1 \
--cnv-exclude hg19_RefGenes.txt \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--out Dup_100_singleton_intergenic

plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-dup \
--cnv-kb 500 \
--cnv-exclude hg19_RefGenes.txt \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--out Dup_500_intergenic

plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-dup \
--cnv-kb 1000 \
--cnv-exclude hg19_RefGenes.txt \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--out Dup_1000_intergenic

plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-dup \
--cnv-kb 9 \
--cnv-max-kb 100 \
--cnv-exclude hg19_RefGenes.txt \
--cnv-indiv-perm \
```

```
--mperm 100000 --within Sex_Batch_cluster.txt \
--out Dup_small_intergenic

plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-dup \
--cnv-kb 9 \
--cnv-max-kb 100 \
--cnv-freq-exclude-above 1 \
--cnv-exclude hg19_RefGenes.txt \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--out Dup_small_singleton_intergenic

# Intergenic deletions
plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-del \
--cnv-kb 100 \
--cnv-exclude hg19_RefGenes.txt \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--out Del_100_intergenic

plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-del \
--cnv-kb 100 \
--cnv-freq-exclude-above 1 \
--cnv-exclude hg19_RefGenes.txt \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--out Del_100_singleton_intergenic

plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-del \
--cnv-kb 500 \
--cnv-exclude hg19_RefGenes.txt \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--out Del_500_intergenic

plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-del \
--cnv-kb 1000 \
--cnv-exclude hg19_RefGenes.txt \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--out Del_1000_intergenic
```

```
plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-del \
--cnv-kb 9 \
--cnv-max-kb 100 \
--cnv-exclude hg19_RefGenes.txt \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--out Del_small_intergenic

plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-del \
--cnv-kb 9 \
--cnv-max-kb 100 \
--cnv-freq-exclude-above 1 \
--cnv-exclude hg19_RefGenes.txt \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--out Del_small_singleton_intergenic

######## Intronic deletions
#### For large deletions
plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-del \
--cnv-kb 100 \
--cnv-intersect hg19_RefGenes.txt \
--cnv-write \
--out Del_100_genic

## Make map file
plink --noweb \
--cnv-list Del_100_genic.cnv --cnv-make-map --out Del_100_genic

plink --noweb \
--cfile Del_100_genic \
--cnv-exclude hg19_Exons.txt \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--out Del_100_intronic

plink --noweb \
--cfile Del_100_genic \
--cnv-del \
--cnv-kb 100 \
--cnv-freq-exclude-above 1 \
--cnv-exclude hg19_Exons.txt \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--out Del_100_singleton_intronic
```

```
plink --noweb \
--cfile Del_100_genic \
--cnv-del \
--cnv-kb 500 \
--cnv-exclude hg19_Exons.txt \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--out Del_500_intronic

plink --noweb \
--cfile Del_100_genic \
--cnv-del \
--cnv-kb 1000 \
--cnv-exclude hg19_Exons.txt \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--out Del_1000_intronic

#### For small deletions
plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-del \
--cnv-kb 9 \
--cnv-max-kb 100 \
--cnv-intersect hg19_RefGenes.txt \
--cnv-write \
--out Del_small_genic

## Make map file
plink --noweb \
--cnv-list Del_small_genic.cnv --cnv-make-map --out Del_small_genic

plink --noweb \
--cfile Del_small_genic \
--cnv-exclude hg19_Exons.txt \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--out Del_small_intronic

plink --noweb \
--cfile Del_small_genic \
--cnv-del \
--cnv-kb 9 \
--cnv-max-kb 100 \
--cnv-freq-exclude-above 1 \
--cnv-exclude hg19_Exons.txt \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--out Del_small_singleton_intronic

######## Intronic duplications
#### For large duplications
```

```
plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-dup \
--cnv-kb 100 \
--cnv-intersect hg19_RefGenes.txt \
--cnv-write \
--out Dup_100_genic

## Make map file
plink --noweb \
--cnv-list Dup_100_genic.cnv --cnv-make-map --out Dup_100_genic

plink --noweb \
--cfile Dup_100_genic \
--cnv-exclude hg19_Exons.txt \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--out Dup_100_intronic

plink --noweb \
--cfile Dup_100_genic \
--cnv-dup \
--cnv-kb 100 \
--cnv-freq-exclude-above 1 \
--cnv-exclude hg19_Exons.txt \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--out Dup_100_singleton_intronic

plink --noweb \
--cfile Dup_100_genic \
--cnv-dup \
--cnv-kb 500 \
--cnv-exclude hg19_Exons.txt \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--out Dup_500_intronic

plink --noweb \
--cfile Dup_100_genic \
--cnv-dup \
--cnv-kb 1000 \
--cnv-exclude hg19_Exons.txt \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--out Dup_1000_intronic

#### For small duplications
plink --noweb \
--cfile Filter_Rare_CNV \
--cnv-dup \
--cnv-kb 9 \
```

```
--cnv-max-kb 100 \
--cnv-intersect hg19_RefGenes.txt \
--cnv-write \
--out Dup_small_genic

## Make map file
plink --noweb \
--cnv-list Dup_small_genic.cnv --cnv-make-map --out Dup_small_genic

plink --noweb \
--cfile Dup_small_genic \
--cnv-exclude hg19_Exons.txt \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--out Dup_small_intronic

plink --noweb \
--cfile Dup_small_genic \
--cnv-dup \
--cnv-kb 9 \
--cnv-max-kb 100 \
--cnv-freq-exclude-above 1 \
--cnv-exclude hg19_Exons.txt \
--cnv-indiv-perm \
--mperm 100000 --within Sex_Batch_cluster.txt \
--out Dup_small_singleton_intronic


#########################################################################
R scripts for logistic regression of global burden of rare CNV
#########################################################################
files<-list.files("input_folder")
for(i in 1:length(files)){
  readpath<-paste("input_folder",files[i], sep="/")
  data<-read.table(readpath,header=TRUE)
  mylogit<-glm(Phenotype ~ NSEG+Sex+Batch, data=data, family = "binomial")
  writepath<-paste("output_folder/GLM_NSEG_OR",files[i], sep="")
  write.table(exp(cbind(OR = coef(mylogit), confint(mylogit))),writepath)
  writepath<-paste("output_folder/GLM_NSEG_p_value",files[i], sep="")
  write.table(summary(mylogit)[["coefficients"]],writepath)
}


#########################################################################
R scripts for heterogeneity test of global burden of rare CNV across cohorts
#########################################################################
library(meta)
beta<-read.table("Beta.txt")
std<-read.table("sd.txt")
beta_m<-as.matrix(beta)
std_m<-as.matrix(std)
for(i in 1:length(beta$V1)){
```

```
print(metagen(beta_m[i,],std_m[i,],method.tau="HE"))
}


##########################################################################
Permutation test of exonic CNVs on individual gene
##########################################################################
#### Test one gene at a time as some genes overlap.
plink --noweb \
--cfile All_filtered_CNVs \
--cnv-intersect Gene_exon_region.txt \
--cnv-write \
--out Gene_Exonic_CNV

plink --noweb \
--cnv-list Gene_Exonic_CNV.cnv \
--cnv-make-map \
--out Gene_Exonic_CNV

plink --noweb \
--cfile Gene_Exonic_CNV \
--cnv-del \
--cnv-intersect Gene_region.txt \
--cnv-test-region \
--mperm 100000 \
--within Sex_Batch_cluster.txt \
--out All_del

plink --noweb \
--cfile Gene_Exonic_CNV \
--cnv-dup \
--cnv-intersect Gene_region.txt \
--cnv-test-region \
--mperm 100000 \
--within Sex_Batch_cluster.txt \
--out All_dup


##########################################################################
R scripts for CMH test of exonic CNVs on individual gene
##########################################################################
cnv_count<-read.table("CNV_count.txt",header=FALSE)
write(paste("Test","Chr","Start","End","Combined_Control","Combined_Case","EMP1","CMH
Odds_ratio","CMH p.value",
"RADIANT_control_male","RADIANT_case_male","RADIANT_control_female","RADIANT_case_female",
"GenRED_II_control_male","GenRED_II_case_male","GenRED_II_control_female","GenRED_II_case_femal
e","GenRED_control_male","GenRED_case_male","GenRED_control_female","GenRED_case_female","NES
DA_NTR_control_male","NESDA_NTR_case_male","NESDA_NTR_control_female","NESDA_NTR_case_f
emale",sep="\t"),"CMH-test.txt", append=TRUE)
for(i in 1:length(cnv_count$V1)){
  try<-c(cnv_count$V9[i],cnv_count$V8[i],724-cnv_count$V9[i],1240-cnv_count$V8[i],
cnv_count$V11[i],cnv_count$V10[i],1736-cnv_count$V11[i],1347-cnv_count$V10[i],
```

```
cnv_count$V13[i],cnv_count$V12[i],139-cnv_count$V13[i],384-cnv_count$V12[i],
cnv_count$V15[i],cnv_count$V14[i],672-cnv_count$V15[i],478-cnv_count$V14[i],
cnv_count$V17[i],cnv_count$V16[i],271-cnv_count$V17[i],743-cnv_count$V16[i],
cnv_count$V19[i],cnv_count$V18[i],670-cnv_count$V19[i],521-cnv_count$V18[i],
cnv_count$V21[i],cnv_count$V20[i],488-cnv_count$V21[i],719-cnv_count$V20[i],
cnv_count$V23[i],cnv_count$V22[i],1080-cnv_count$V23[i],1194-cnv_count$V22[i])
  dim(try)<-c(2,2,8)
  dimnames(try) = list(Phenotype = c("Case", "Control"), cnv = c("Yes", "No"),Array =
c("RADIANT_Illumina_male","RADIANT_Illumina_female",
"GenRED_II_male","GenRED_II_female","GenRED_male",
"GenRED_female","NESDA_NTR_male","NESDA_NTR_female"))
  CMH_output<-mantelhaen.test(try,exact=TRUE,alternative="greater")

write(paste(cnv_count$V1[i],cnv_count$V2[i],cnv_count$V3[i],cnv_count$V4[i],cnv_count$V6[i],cnv_count$
V7[i],cnv_count$V5[i],CMH_output[["estimate"]][["common odds
ratio"]],CMH_output[["p.value"]],cnv_count$V8[i],cnv_count$V9[i],cnv_count$V10[i],cnv_count$V11[i],cnv
_count$V12[i],cnv_count$V13[i],cnv_count$V14[i],cnv_count$V15[i],cnv_count$V16[i],cnv_count$V17[i],cn
v_count$V18[i],cnv_count$V19[i],cnv_count$V20[i],cnv_count$V21[i],cnv_count$V22[i],cnv_count$V23[i],s
ep="\t"),"CMH-test.txt", append=TRUE)
  rm(try)
  rm(CMH_output)
}



#########################################################################
Permutation test on segment groups
#########################################################################
plink --noweb \
--cfile Filtered_rare_deletions \
--segment-group \
--out Del_groups

plink --noweb \
--cfile Filtered_rare_duplications \
--segment-group \
--out Dup_groups

plink --noweb \
--cfile Del_all \
--cnv-intersect Deletion_segment-group_region.txt \
--cnv-test-region \
--mperm 100000 \
--within Sex_Batch_cluster.txt \
--out Del_segment_test

plink --noweb \
--cfile Dup_all \
--cnv-intersect Duplication_segment-group_region.txt \
--cnv-test-region \
--mperm 100000 \
--within Sex_Batch_cluster.txt \
```

--out Dup_segment_test

```
##########################################################################
R scripts for CMH test on segment groups
##########################################################################
cnv_count<-read.table("Breakdown_count.txt",header=FALSE)
write(paste("Test","Chr","Start","End","Combined_Control","Combined_Case","EMP1","CMH
Odds_ratio","CMH p.value",
"RADIANT_control_male","RADIANT_case_male","RADIANT_control_female","RADIANT_case_female",
"GenRED_II_control_male","GenRED_II_case_male","GenRED_II_control_female","GenRED_II_case_femal
e","GenRED_control_male","GenRED_case_male","GenRED_control_female","GenRED_case_female","NES
DA_NTR_control_male","NESDA_NTR_case_male","NESDA_NTR_control_female","NESDA_NTR_case_f
emale",sep="\t"),"CMH-test.txt", append=TRUE)
for(i in 1:length(cnv_count$V1)){
  try<-c(cnv_count$V9[i],cnv_count$V8[i],724-cnv_count$V9[i],1240-cnv_count$V8[i],
cnv_count$V11[i],cnv_count$V10[i],1736-cnv_count$V11[i],1347-cnv_count$V10[i],
cnv_count$V13[i],cnv_count$V12[i],139-cnv_count$V13[i],384-cnv_count$V12[i],
cnv_count$V15[i],cnv_count$V14[i],672-cnv_count$V15[i],478-cnv_count$V14[i],
cnv_count$V17[i],cnv_count$V16[i],271-cnv_count$V17[i],743-cnv_count$V16[i],
cnv_count$V19[i],cnv_count$V18[i],670-cnv_count$V19[i],521-cnv_count$V18[i],
cnv_count$V21[i],cnv_count$V20[i],488-cnv_count$V21[i],719-cnv_count$V20[i],
cnv_count$V23[i],cnv_count$V22[i],1080-cnv_count$V23[i],1194-cnv_count$V22[i])
  dim(try)<-c(2,2,8)
  dimnames(try) = list(Phenotype = c("Case", "Control"), cnv = c("Yes", "No"),Array =
c("RADIANT_Illumina_male","RADIANT_Illumina_female",
"GenRED_II_male","GenRED_II_female","GenRED_male",
"GenRED_female","NESDA_NTR_Affy_male","NESDA_NTR_Affy_female"))
  CHM_output<-mantelhaen.test(try,exact=TRUE,alternative="greater")

write(paste(cnv_count$V1[i],cnv_count$V2[i],cnv_count$V3[i],cnv_count$V4[i],cnv_count$V6[i],cnv_count$
V7[i],cnv_count$V5[i],CHM_output[["estimate"]][["common odds
ratio"]],CHM_output[["p.value"]],cnv_count$V8[i],cnv_count$V9[i],cnv_count$V10[i],cnv_count$V11[i],cnv
_count$V12[i],cnv_count$V13[i],cnv_count$V14[i],cnv_count$V15[i],cnv_count$V16[i],cnv_count$V17[i],cn
v_count$V18[i],cnv_count$V19[i],cnv_count$V20[i],cnv_count$V21[i],cnv_count$V22[i],cnv_count$V23[i],s
ep="\t"),"CMH-test.txt", append=TRUE)
  rm(try)
  rm(CHM_output)
}
```